A DISSERTATION

ON

PROSPECTIVE STUDY OF INCIDENCE, CLINICAL PROFILE & OUTCOME OF ACUTE KIDNEY INJURY IN PATIENTS WITH SNAKE BITE ENVENOMATION ADMITTED IN GMKMCH, SALEM

Submitted to

THE TAMILNADU DR. M. G. R. MEDICAL UNIVERSITY,
CHENNAI

In partial fulfillment of the regulations
for the award of

M. D. DEGREE IN GENERAL MEDICINE
BRANCH I

GOVERNMENT MOHAN KUMARAMANGALAM
MEDICAL COLLEGE, SALEM
APRIL 2017

Government Mohan Kumaramangalam Medical College Hospital

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation titled "**PROSPECTIVE STUDY OF INCIDENCE, CLINICAL PROFILE & OUTCOME OF ACUTE KIDNEY INJURY IN PATIENTS WITH SNAKE BITE ENVENOMATION ADMITTED IN GMKMCH, SALEM"**is a bonafide and genuine research work carried out by me under the guidance of***DR. S. RAMASAMY, M. D.,* Professor, Department of General Medicine and under the co guidance of***DR.P.NAGARAJAN, M. D., D.M (Nephro***), Professor and Head, Department of Nephrology, Government Mohan Kumaramangalam Medical College Hospital, Salem, Tamil Nadu, India.

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Acknowledgement

I am extremely thankful to **Dr. P. KANAGARAJ, M.D.**, Dean, Government Mohan Kumaramangalam Medical College Salem, for allowing me to utilize the hospital facilities for doing this work.

I express my immense gratitude to **Dr. S. RAMASAMY, M. D.,** Professor, Department of General Medicine, Government Mohan Kumaramangalam Medical College Hospital, for his unrelenting inspiration and excellent guidance in the completion of this study. His enthusiasm and immense encouragement have been responsible for easing out many

shortcomings during this work

I am deeply indebted to **Dr. P. NAGARAJAN M.D., D.M.**, Professor & Head, Department of Nephrology, Government Mohan Kumaramangalam Medical College Hospital, for his fathomless enthusiasm and motivation throughout the study.

I would like to express my heartfelt gratitude to my postgraduate mentor and teacher, **Dr.S.R.SUBRAMANIAN M.D.,** Professor& Head, Department of General Medicine, Government Mohan Kumaramangalam Medical College Hospital for his relentless encouragement and expert guidance throughout the period of the study and postgraduate course.

Warmest and sincere thanks to my Professors - **Dr. V.SUNDARAVEL M.D., Dr.T.RAVIKUMAR M.D., Dr. S. SURESHKANNA M.D.,** and **Dr. D. VIJAYARAJU M.D.,DR.A.EZHILARASII M.D, D.M (Nephro)** for all the help, encouragement and guidance during my post graduation study period.

My warmest gratitude to **Dr. J. A. VASANTHA KUMAR M.D.,** Registrar, Department of General Medicine for his guidance in completing the study.

I would like to express my gratitude to **Dr. M. LOGANATHAN M.D., Dr.N .KALAISEZHIAN M.D.,Dr.A. PRABHU M.D.,** whose relentless encouragement inculcated in me a sense of confidence.

I am deeply grateful to **Dr. C.ANANDHI M.D.,Dr. T.YOGANANDH M.D., Dr.M.RAJKUMAR M.D., Dr.S.SUDHASELVI M.D.,Dr.M.KUMAR RAJA M.D.,**and **Dr.P.ARUL M.D.,**Assistant professors in the Department of General Medicine for their immense help and guidance during my post-graduation course. I am also thankful to all the Assistant professors for their continued guidance throughout my study period.

I would like to thank **Dr. M.SEENIVASAN M.D, D.M,** Assistant professor, Department of Nephrology for his support throughout this study.

I would like to acknowledge **Dr. A.VIKNESH AMBAYIRAM**, for helping me to analyze and compile the statistical data for my study.

I extend my heartfelt thanks to all my colleagues and friends for their help rendered

during my study.

I specially thank all my patients without whose cooperation, this dissertation would never have seen the light of the day.

ABBREVIATION

AKI - Acute Kidney Injury

AKIN - Acute Kidney Injury Network

ARDS - Acute Respiratory DistressSyndrome

ARF - Acute RenalFailure

ASV - Anti Snake Venom

ATN - Acute TubularNecrosis

aPTT - Activated Partial ThromboplastinTime

BT - BleedingTime

BUN - Blood Urea Nitrogen

CRF - Chronic RenalFailure

CT - Clottingtime

CT KUB - Computerized Tomography- KUB

CVP - Central VenousPressure

DIC - Disseminated IntravascularCoagulation

ECG - ElectroCardioGram

IgE - Immuno Globulin E

IV - IntraVenous

FDPs - Fibrin Degradation Products

FFP - Fresh FrozenPlasma

Hb - Hemoglobin

KUB - Kidney, Ureter, Bladder

LDH - Lactate Dehydrogenase

MOSF - Multi Organ SystemFailure

PCV - Packed CellVolume

PT - Prothrombintime

RBC - Red Blood Cell

RBS - Random BloodSugar

RIFLE - Risk, Injury, Failure and End stage Renal Disease

SAE - South East Asian Countries

USG - Ultra Sono Gram

WBCT - Whole Blood Clotting Time

WHO - World Health Organization.

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abstract

ABSTRACT

Background and objectives:

A study of incidence of Acute Kidney Injury, Clinical profile and Investigations of patients admitted with snake bite and systemic envenomation and an analysis of the outcome of these patients in response to multiple factors. The study also determines if there is any age or sex predilection for the severity of envenomation.

Materials and methods:

100 cases admitted at Government Mohan Kumaramangalam Medical college Hospital, Salem, during the period April 2015 to March 2016, with clinical evidence of snake bite envenomation were included in the study after taking into account the inclusion and exclusion criteria. Out of the 100 cases 56 were males and 44 were females. All the 100 cases were treated for snake envenomation and their laboratory work up and follow up data were collected and studied.

Results:

44% of Snake bite victims have developed Acute Kidney Injury. Delay in admission was strongly correlated with development of Severe AKI ($P<0.0005$). Victims with co-morbidities are more prone

to develop AKI and Complications. Most of the patients with AKI (93%) had Cellulitis and Lymphadenopathy (P<0.05). AKI is uncommon in Patients without coagulopathy. Thrombocytopenia and Albuminuria can be taken as early markers of Severe Envenomation (P<0.0005) and Acute Kidney Injury (P<0.0005) respectively. 80% of patients were required conservative management only. 90% of AKI Patients recovered completely (P<0.0005). Only 6 patients of Stage 3 AKIN (24%) become dialysis dependent. 4 patients in AKIN3 group (16%) died due to complications of AKI (P<0.0005). People who were initiated on prompt medical therapy earlier and follow up showed signs of early recovery and favorable prognosis. This was also corroborated with the laboratory work up results of these patients.

Interpretation and Conclusion:

Early admission to the hospital and early administration of Inj.ASV with adequate supportive therapy is important to prevent development severe Acute Kidney Injury and its complications. The morbidity and mortality is high if severe cellulitis is associated with prolonged coagulopathy .

Key Words: Snake Bite, ASV, Acute Kidney Injury, Hemotoxicity.

introduction

INTRODUCTION

Snake bite envenomation is a significant cause of mortality and morbidity in tropical as well as subtropical countries like Indian subcontinent. Envenoming by poisonous snakes is an occupational hazard commonly occurs in farmers and people living in rural and forest areas.The habit of moving out about bare footed in these areas contribute to its higher incidence. It is a leading cause in premature death in rural India[1].

It causes two types of toxicity, hemotoxicity and neurotoxicity depends upon the snake which bites. Acute renal failure can occur with the bite of any venomous snake.It is more common with snakes of the viperine species. The worldwide published statistics on the incidence of Acute Kidney Injury (AKI) following venomous snake bite in developing countries like India are inadequate as a proportion of the victims resorting to traditional means of therapy often resulting in deaths[5].

The Annual global mortality from snake bites is estimated at around 94000 Per year with around 15000 deaths occurring per year in India alone[4].

The incidence of Acute Renal Injury in India is 20-32% following viper bite.There is wide spread discrepancy with the data available on the Incidence of Acute Renal injury caused by Snake bite envenomation[14]

Early administration of appropriate anti-snake venom is the specific treatment in snake envenomation. Early Complete neutralization of effects of venom will cause zero morbidity and mortality, but this is not actually happens.

Salem city is surrounded by hills; Nagarhills on the north, Jaruguhills on the south,Shevaroy hills on the northeast,Goduhills on the east and Kariyaperumal hills in the southwestern. The Cauvery river flows through the district and the Mettur dam was built across the river. So Agriculture is the principal means of livelihood inSalem and itsnear by districts. The district is heavily infested with venomous snakes, and the victims of snake bite are mostly healthy youngpersons mostly belonging to the lower socio-economic strata, most of them bread winners of the family.

THE GOVERNMENT MOHAN KUMARAMANGALAM MEDICAL COLLEGE HOSPITAL is one of the best Multispeciality government hospitalin Tamilnadu. It receives Patients from 6 districts (Salem, Namakkal,Erode, Trichy,Villupuram,Dharmapuri,Krishnagiri) in the North-western Tamilnadu.

The study has been conducted to assess incidence of acute kidney injury and it’s clinical, haemodynamic and investigation profiles and outcome of patients admitted with snakebite and systemic envenomation in GMKMC HOSPITAL, SALEM.

AIMS
And
OBJECTIVES

AIMS & OBJECTIVES OF STUDY

This is a prospective study of snakebite with systemic envenomation

- To study the incidence of acute kidney injury, Clinical, hemodynamic and investigation profiles of patients admitted with snakebite and systemicenvenomation.
- To analyse the outcome of patients in relation to multiple factors like bite and needle time, amount of Inj.ASV administered and other factors.
- To know whether there is any age or sex predilection for the severity of envenomation.
- To define and classify Patients with AKI according to AKIN staging and to know causative factors for development of AKI.
- To know outcome of Patients with AKI with various managements.
- 100 Patients admitted in various medicalwards from 1.04.2015to31.03.2016 were taken up for the study.

Review of literature

REVIEW OF LITERATURE

HISTORICAL ASPECTS

Snakes are elongated, legless carnivorous Reptiles of the suborder Serpentines, which do not have eyelids and external ears. Their apparent renewal of life with casting of skin and the power of some of them to inflict suffering and death have given them a supernatural aura which made them worthy of worship by some ethnic groups. In Indian mythology, Cobra was worshipped as Naga. "Aadishesha on whom Vishnu does yoga nidra, Vasuki is the king of Nagas, Kaliya poisoned the Yamuna river where he lived,Krishna subdued Kaliya and compelled him to leave the river, Manasa is the queen of the snakes are wonderful tales of famous snakes in Indian mythology". In ancient Greek, it was believed that "**Aesculapius** would crawl across the bodies of sick people asleep at night in his shrines and lick them back to health". In India, snake bite was treated by many cruel methods like making local incisions, pricks, punctures, attempting to suck the venom bit bite mark, using snake stones and application of chemicals, herbals on the bite mark. The most important landmark in the treatment of snake envenomation was the development of anti-snake venom. It was prepared by Albert Calmette in 1890, when his village flooded and monocled cobras killed more than 40 people in his village[4]. Hence he caught a few snakes, milked them of their venom and injected into horses to create antibodies. Other prominent

names in the development of anti snake venom are Acton, Knowll and Fraser. Ahiya M.L found that antivenom to Indian cobra was effective against South African cobras.Lamb and his successors produced antivenom against Russell's viper in India.[6] Later came the polyvalent antivenomfrom the central research institute, Kasauli. The Later developments were supportive measures like dialysis and blood component therapy. Latest trends are rapid immunodiagnostics and administration of specific monovalent anti venom, development of antivenom against locally seen snakes and development ofvaccine.[7,8]

EPIDEMIOLOGY

Snakes do not ordinarily prey on humans. Unless it was startled or injured, most of the snakes preferred to avoid contact with humans. “Snakebite is one of the most neglected public health issues in poor rural communities living in the tropics”[20]. Most snakebites are occurred on the lower limb of agricultural workers and children living in rural areas. Since in developing countries like India where” the majority of the victims are initially treated by professional snake healers, snake charmers and religious men who use herbal remedies, ‘mantras’ and apply snake stone to the wound, all of which are supposed to magically draw out the venom from the victim”[9] In India ,46000 people (99% CI 41000-51000) die from snakebite each year, a figure based on verbal autopsy of all deaths in 6671 randomly chosen sample areas throughout the country[26]- (Mohapatra B 2011). Snake bite was responsible for 0.5% of all deaths, 97% of the victims died in rural areas, only 23% in health facility[32].

No significant difference in the severity of snake envenomation was reported between males and females, even though, the male to female ratio of bite varied from 3:1 to 4:3 in various studies. The study from Gujarat also reports that more bites occur during daytime (7:3) but there is no mention about diurnal variation of severity of bite. Krait is a nocturnal snake, so majority of the bite will around 12am to 4 am, most of the patients will be unaware of the bite, presented with neurotoxicity in the

morning, often misdiagnosed as cerebro vascular accidents[22].

In rural areas, Victims often do not find the species of snake or misdiagnose to another species, especially Cobra. This is common with female and children. Due to poor knowledge regarding snakes, poor visibility, frightness on seeing the snakesetc.leads to poor identification of snakes[18].

SNAKE BITE IN INDIA

The numbers of snake-bite fatalities in India has long been controversial. "It was Estimated as low as 61 507 bites and 1,124 deaths in 2006and 76,948 bites and 1,359 deaths in 2007 [Government of India data: P 108 of *http://cbhidghs.nic.in/writereaddata/mainlinkFile/Health%20Status%20Indicators.pdf*) and as high as 50 000 deaths each year have been published and the Registrar-General of India's "Million Death Study", 2001-2003, is expected to provide reliable evidence of substantial mortality (exceeding 50 000 per year) as it is based on **R**epresentative, **R**e-sampled, **R**outine **H**ousehold **I**nterview of **M**ortality with **M**edical **E**valuation (RHIME), covering all age groups across the entire country with geographical, seasonal and occupational data."In 1992, Hati et al did a large field survey in the villages of Burdwan district of West Bengal revealed that every year 8000 people were bitten by snakes, among them 800 peoples died[11].

SNAKES

Of the 3346 species of snakes are identified in the world over, but only 667 of these having fangs ventrally, can inject the venom while biting human or animals.. In India there are about 242 species of snakes of which 57 are poisonous[21] and belong to the family of Eliapidae, Colubridae, and Viperidae. Bites of Viperidae, Crotalidae and Colubridae usually have hemostatic abnormalities and features of local envenomation. The Elapidae is commonly producing neurological signs like descending paralysis and Hydrophidae causes Rhabdomyolysis. The carpet or saw scaled viper (EchisCarinatus) justifiably is one of the most dangerous snake in the world.[7,8]

VENOMOUS SNAKES

Venomous snakes are of 3 families

ATRACTASPIDINAE – also called adders or false vipers. Very long solenoglyphous(hinged erectile fangs). Also called side stabbing/stiletto snakes, because they attack their victims by side swiping motion, and the fangs are protruding from the corner of the partially closed mouth[7].

ELAPIDAE – short fixed proteoglypous (short fixed fangs). This includes cobras, kraits, mambas, coral snakes and sea snakes.

VIPERIDAE - This includes old world vipers and pit vipers. Old world

vipers have long curved hinged fangs in the front which contains a closed venom channel. Pit vipers has an infrared heat sensitive organ to identify warm blooded animals.

OTHER NON-VENOMOUS SNAKES:

BORDAE FAMILY – called the giant constrictors and known for swallowing the victims. Examples: Reticulated pythons, African rock pythons, South American anaconda, Australian serous Python.

COLUSRIDAE FAMILY – largest family of snakes, includes 1748 species.

The quantity of venom injected every first bite of snake and fatal dose for men varies in different snakes. Sometimes 1/6 of amount of venom is fatal for healthy human. For e.g. Cobra bite.

Table.1. Dry weight and fatal dose of venom of various snake Species[4].

Snake species	**Dry weight of venom (mg)**	**Fatal dose (mg)**
Spectacled Cobra	60	12
Krait	20	6
Russell Viper	63	15
Saw scaled Viper	13	8

WHO categorized poisonous snakes of India according to the severity of envenomation treated with more importance as follows[4].

WHO - MEDICALLY IMPORTANT SNAKES IN INDIA

Category 1:	**Elapidae:** *Bungarus caeruleus; Naja kaouthia* (north-east), *Naja naja* (throughout) **Viperidae:** *Daboia russelii, Echis carinatus; Hypnale hypnale* (south-west)
Category 2:	**Elapidae:** *Bungarus fasciatus, Bungarus niger, Bungarus sindanus, Bungarus walli; Naja oxiana* (north-west), *Naja sagittifera* (Andaman Islands); *Ophiophagus hannah* (south, north-east, Andaman Islands); **Viperidae:** *Cryptelytrops albolabris, Cryptelytrops purpureomaculatus* (east), *Trimeresurus malabaricus* (south-west), *Trimeresurus gramineus* (south India, Andaman & Nicobar Islands), *Macrovipera lebetina* (north-west).

THE BIG FOUR SNAKES

COMMON COBRA :

Zoological Name : NajaNaja

Family **:**Elapidae

Location **:** Commonly seen in India, Pakistan, Bangladesh, Nepal. In India, it is abundantly seen in Assam & Kashmir.

Tamil Name **:** ***நாகப்பாம்பு/நல்லபாம்பு***

Appearance **:**Ventral scales may be grey, yellow, black or brown. Dorsal scales may bear a hood mark or sometimes salt & pepper speckles may be seen. When hood is present 2 circular ocelli patterns get connected by a curved line resembling a spectacle. It is of length 1 – 1.5m.

Identifying Features: It expands the head when threatened and forms hood. In the dorsal aspect of hood, spectacle shaped mark will be present.

INDIAN KRAIT (BLUE KRAIT) :

Zoological Name: BungarusCaeruleus

Family : Elapidae

Tamil Name **:** ***கட்டுவிரியன்***

Location: Commonly seen in south India & Sri Lanka.

IMAGES OF ELAPIDAE SPECIES

Figure 2.1. SPECTACLED COBRA WITH HOOD

Figure 2.2. COBRA WITH SPECTACLE

Figure 2.3 DORSAL SURFACE OF KRAIT

Figure 2.3. VENTRAL ASPECT OF INDIAN KRAIT

Appearance : Head is flat with hardly evident neck. The head shields are normal with no laurels. It is generally black in colour with white crossbars in the dorsal side. The ventral part (belly) of the snake is pure white in colour without scales.

Behaviour : During day it is sluggish & generally inactive whereas at night it is active & escapes from rodent holes or loose soil by hissing loudly. When it was agitated, it will make coils and insert the head into the coils &body become flatten.

RUSSELL'S VIPER (CHAIN VIPER / SEVEN PACER / SCISSOR SNAKE) :

Zoological Name: DabioaRusselli

Family : Viperidae

Location: Commonly seen in India, Pakistan, Sri Lanka, Bangladesh, Nepal, and Thailand. In India, it is seen abundantly in Punjab, along West coast & its hills, in southern India & North to Bengal.

Tamil Name :***கண்ணாடிவிரியன்***

Appearance : It has a triangular head & the crown of which bears irregular strongly fragmented scales. Dorsal scales are highly keeled & the ventral scales are 153 – 180 in number. The head has a pair of distinct dark patches one on each temple with brownish V or X marking to form

an apex. The maxillary bones bear around 2-6 pairs of fangs at a time with 1st being active & the others being replacements. Maximum length of this type is around 5.5 feet.

Identifying feature: It behaves as a nocturnal forager but during winter it becomes active during day time. When threatened it forms a series of S loops, raise the proximal third of the body & produce a hiss.

SAW SCALED VIPER:

Zoological Name:Echiscarinatus.

Family : Viperidae

Tamil Name : **சுருட்டைவிரியன்**

Location : India, Pakistan, Sri Lanka, Bangladesh.

Appearance : The head is distinct from neck covered with dorsal keeled scales & ventral rounded scales. Colour pattern – pale buff, greyish or reddish with series of variably coloured spots with lighter interblotch patches.

Behaviour:It is mostly crepuscular & nocturnal. Most active after rains or on humid nights. Typical pose – a double coil with figure of eight with head poised in the centerpermitting it to lash out like a released.

POISONOUS SPECIES OF VIPERIDAE FAMILY

Figure 3.1 Dorsal aspect of Russell viper

Figure 3.2 Ventral aspect of Russell Viper

Figure 3.3. SAW SCALED VIPER

IMAGES OF POISONOUS AND NON-POISONOUS SNAKES OTHER THAN BIG FOUR SNAKES

Figure 4.1. KING COBRA Figure 4.2. HUMP NOSED PIT VIPER

COMMON NON- POISONOUS SNAKES IN INDIA

Figure 4.3.RAT SNAKE Figure 4.4. INDIAN ROCK PYTHON

SNAKE VENOM

Snake venom is protein in nature, contains so many polypeptides,enzymes and coagulant and anticoagulant substances.Itisrich bio-resource of biologically active compounds, identification and characterization of toxic compounds present in each snake venom is the main step not only to understand the pathophysiological changes but they can also be useful to improve the treatment after snake bite[43].

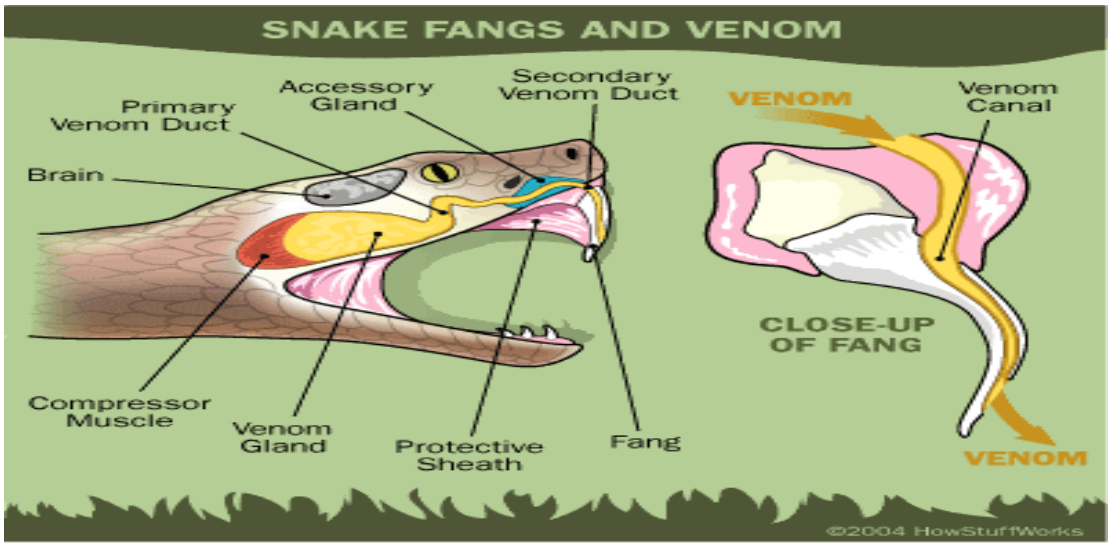


Fig.4) Snake venom apparatus

NATURE OF VENOM:

PHYSICAL APPEARANCE:

Snake venom is a clear, transparent, pale yellow or straw-coloured viscous fluid. It is thermos labile; having a specific gravity of 1.03-1.07.The pH of the venom varies in different species and also when they exposed to sun, they turns slightly turbid[34] .It can be dried as crystals or lyophilized and dried venom is thermo-stable**.It is soluble in**

waterandglycerine. It is destroyed by coagulating agents like $KMnO_4$, $AgNO_3$, as well as alcohol and strong alkalies like NaOH and KOH, etc[46].

Fig.5). Physical appearance of Snake Venom

BIOCHEMICAL CONSTITUENTS OF SNAKE VENOM ;

Snake venom contains varying proportions of enzymes, non enzymatic toxins, nontoxic proteins and acetyl choline.

Enzymes:

Enzymes constitute about 10 – 90 % of viperid and 25 – 75 % of elapid venoms. Various enzymes of snakes are discussed below.

Proteinases: They cause significant tissue changes and destruction because of the digestion of tissue protein and peptides. Enzymes liberate histamines from the damaged endothelium which leads to dissolution of blood vessels.

Hyaluronidases: This enzyme helps in the rapid diffusion of venom from

the site of bite by hydrolysis of hyaluronic acid present in the connective tissue.

Acetyl Choline Esterase: Formed mainly in elapid venom, it facilitate the cleavage of acetyl choline to acetic acid and choline, which leads to impairment of neuromuscular transmission[46].

Phospholipase: Phospholipase A_2 has a direct hydrolysing action on the cell membrane and indirectly produces haemolytic agents like lysolecithin, hence facilitating haemolysis.

Phosphodiesterase: Ittargets the DNA, RNA and nucleotide derivatives. This is responsible for the fall in systemic arterial pressure[55].

Acetyl choline: It has the direct cardiac action or on neuromuscular junction.

Metalloproteinases : It causes disruption of the endothelial lining and is the main cause of cellulitis[7].

PRO COAGULANTACTIVITIES:

Snake venom contains many Procoagulants which interact at coagulation cascade and activate coagulation mechanisms which results in formation micro thrombi (DIC like mechanism) and consumption coagulopathy which is the cause for prolonged clotting time in Snake bite[8].

Direct prothrombin activator:

This unnamed substance which directly activates of prothrombin of Human And Bovine does not requires any activation , cleaves one or more peptide bonds, which generate a catalytically active intermediate which undergoes auto conversion to thrombus.

This mechanism is also observed with Elapid,Viperid and Colubride venom bite,not in the case of Crotalids.

Factor V activator:

A specific peptide in Russell Viper venom activates Factor V and activates Clotting cascade.

Factor X activator:

Macfarlane discovered that a specific substance which present in Russell Viper venom activates Factor X in the presence of Calcium, which induces a conformational changes in Factor X^{14}.

Factor IX Activator:

Factor X activator presents in the Russell Viper also activates Factor IX also.

Indirect prothrombin Activator:

This factor along with Activated factor X convertsprothrombin to Thrombin which is the prime material of thrombus formation.

Thrombin like Peptides:

Venom of Viperidae contains some Glycopeptides, which cannot be

inhibited by direct thrombin inhibitor like Heparin. This enzymes release Fibrinolytic peptide A&B,which directly activates thrombin[34].

ANTI-COAGULANTACTIVITIES:

Snake venom contains anti coagulants in addition to pro coagulants, they causes anticoagulation by following mechanisms:

- Inhibition of one or more clotting factor or prevention of activation of clotting factor.
- Directly activating on Fibrinogen and causes Fibrinolysis.
- Activation of plasminogen or proactive Plasminogen directly which causes fibrinolysis.

NON-ENZYMATIC POLYPEPTIDE TOXINS PROTIENS:

Toxins in snake venom is broadly classified into two groups- neurotoxins and hemotoxins, but there are more than two types of toxins they are myotoxin , cardiotoxins.no venom contains one type toxins, most snake have combination of toxins.

HEMOTOXINS:

Toxin acts by lysing erythrocytes , it disrupts blood clotting processes, also severely damages the internal organs and other tissues. Generally these toxins acts slower than neurotoxins. Toxins of most vipers and many cobra species are hemotoxins[2].

CARDIOTOXIN:

These specifically binds to myocardial cells and increase cellular depolarisation and resulted in inhibition of contraction of heart.

The toxins sometimes release calcium from surface membrane of myocardium resulted in cardiac arrest.

Some of substances increase vascular leak producing "Capillary Leak Syndrome" which causes intravascular hypovolemia and third space fluid collection, all resulted in shock[4].

NEUROTOXINS:

Neurotoxins are low molecular weight exclusively found in Elapidae species, also in Hydrophid,Vipridae,Crotalid venoms. It is fast acting toxins. Neurotoxins fall in two groups they are postsynaptic neurotoxins:

POST SYNAPTIC BLOCKING TOXINS :

Alpha-neurotoxins such as alpha-Bungarotoxins and Cobratoxins are a large group, binds to the Nicotinic acetylcholine receptors of cholinergic neurons present in motor end-plates of skeletal muscle, since they mimic the shape of the acetylcholine molecule and it binds to the receptors and block the acetylcholine flow which leads to feeling of numbness and paralysis.

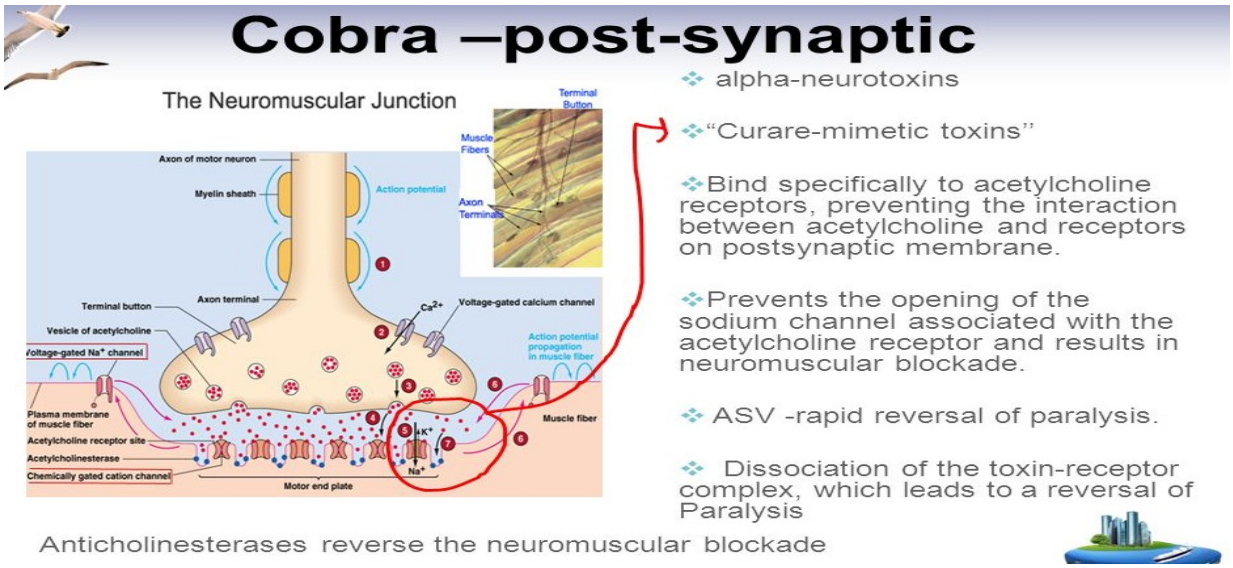


Fig. 6).Neuro muscular blockade mechanism of cobra venom.

PRESYNAPTIC NEUROTOXINS:

Beta-neurotoxins or presynaptic phospholipases A2 such as beta-bungarotoxins, crotoxin, taipoxin.Presynaptic neurotoxin produces neuromuscular blockade by inhibiting acetylcholine release from presynaptic membrane and causes progressive flaccid paralysis[8].

FASCICULINS:

Theseare synergistic neurotoxins, inhibits acetylcholine Esterasesresults in accumulation of Ach this cause severe, generalized and long-lasting (5-7 h) fasciculations (rapid muscle contractions),which may leads to death.Mostly it found in mambas and some rattle snakes.

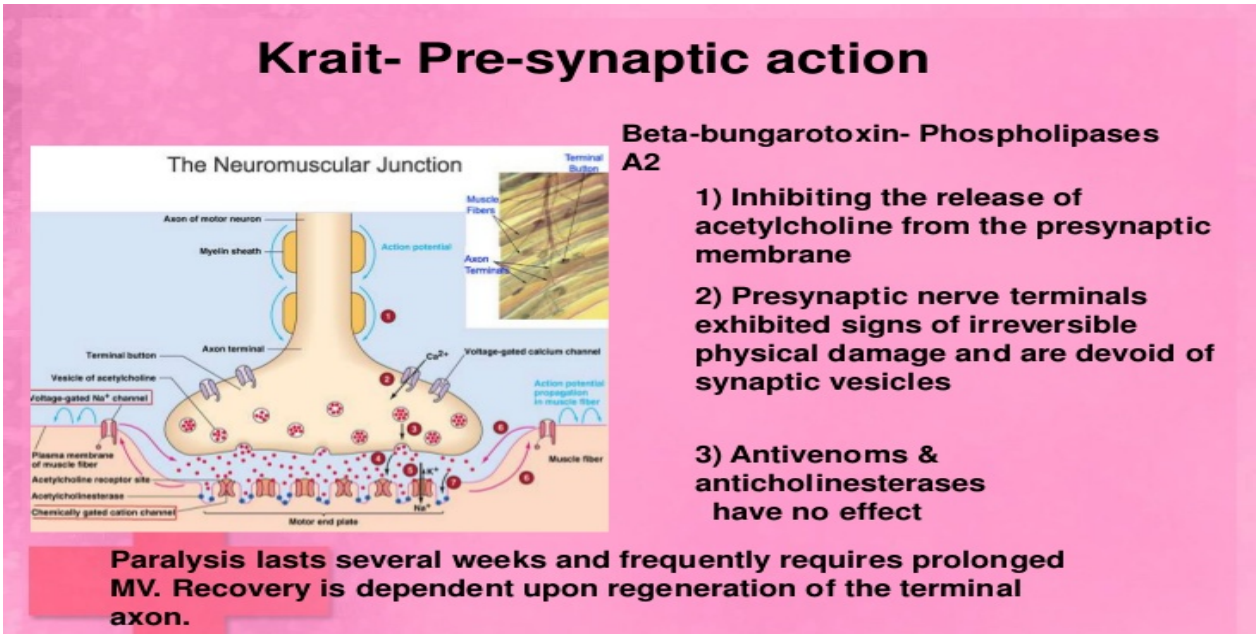


Fig. 7).Neuro muscular blockade mechanism of Krait Venom

DENDROTOXINS:

Dendrotoxins also an synergistic toxins which inhibit neurotransmissions by binding tovoltage-gated potassium channels and blocking the exchange of positive and negative ions across the neuronal membrane lead to no nerve impulse, thereby paralysing the nerves.it also seen *mambas* .k-bungarotoxins, which bind to somespecific nicotinic acetylcholine receptors in the brain andvarious ganglia.

CYTOLYSINS:

It causes lysis of cell structures of blood and tissue, resulting in swelling, cellulitis, bleb formation and rarely necrosis[11].

SYMPTOMATOLOGY

GENERAL SYMPTOMS:

SYMPTOMS NOT RELATED TO ENVENOMATION

The snake bite victims will develop frightness, anxiety, palpitations, syncopal attack as thought of death or consequences of snake bite envenomation.

Some of the patients will develop anxiety, hyperventilation, increased sweating which may confuse with systemic manifestations of Neurotoxic snake bites.

Native irrational treatment done by traditional healers or relatives like incision over bite mark, application of irritants, Plant juices etc which may produce irrational symptoms and signs which may mislead our diagnosis and management.

Other common symptoms are headache,Nausea, vomiting, abdominal colicky, drowsiness, fatigability.

LOCAL SYMPTOMS:

- Fang or bite marks of snake
- Pain at the bitten area
- Swelling
- Bleeding from Fang marks
- Bruising
- Localised tender lymphadenopathy
- Bullae formation,

- Local infection, Necrosis, Gangrene.

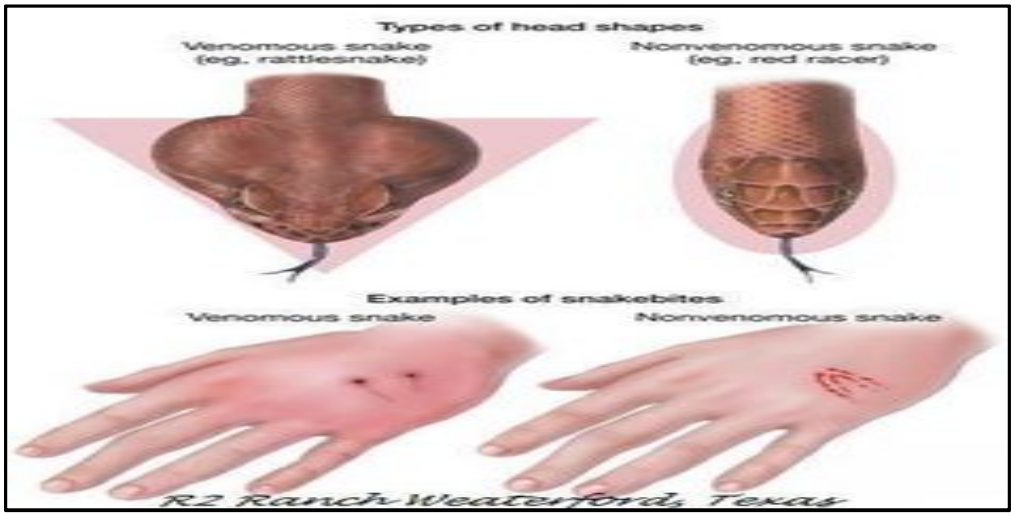


Fig. 9). Bite marks of Poisonous and Non-Poisonous Snakes

SYSTEMIC SYMPTOMS:

It depends upon the species of snake which bites and amount and potency of venom injected. Most of the times the symptoms and signs will correlate with species of snake if it was identified, hence the species of snake can be retrospectively identified with patient's description, circumstances of bite and the features of envenomation.

Figure.10. General symptoms of snake bite envenomation

VIPERID ENVENOMATION

LOCAL ENVENOMING:

Venoms of vipers and pit vipers produce severe local effect. It is mainly hemotoxic and also will produce neurotoxic manifestations rarely.

1. PAIN

When the snake bites, the fang will pierce the skin, subcutaneous tissue which will produce pain initially, it may disappear if the snake didn't inject the venom in case of dry bite or non poisonous snake.

The venom itself is a irritant and also contains so many proteases and metalloproteinases which cause tissue damage, inflammation which will produce continuous pain.

Ascending cellulitis, lymphangitis, rapidly forming swelling and accumulation of fluid, vascular occlusions, secondary bacterial infections and ischemia, gangrene formation and compartmental syndrome are the causes for excruciating continuous pain in snake bite envenomation.

2. SWELLING OF BITTEN AREA:

Viper's venom will produce severe local effect. Swelling usually appears within 15 minutes, but rarely is delayed for several hours. It spreads rapidly, sometimes to involve the whole limb and adjacent trunk. If the swelling is rapidly evolving it can be used to assume as Viper envenomation, if the snake was not identified. Patient will also have

painful, tender localised lymphadenopathy. Bruising, especially in path of superficial lymphatics, also over the regional lymph nodes, is common. Swollen limbs can accommodate many litres of extravasated blood, leading to hypovolemic shock. Most viper venoms are predominately vasculotoxic causing localised swelling around the bite mark, is due to diffusion of venom through the superficial tissue. Venom metalloproteinase hemorrhagins, membrane damaging polypeptide toxins, phospholipases, and endogenous autacoids such as histamine, serotonin and kilims are responsible.

The swelling part will be shiny with stretched skin. It will tender on palpation and will extend centripetally may extend up to groin from foot, up to axilla in case of bite in the hands. Sometimes it may spread to opposite part of the body in case of severe envenomation caused byVipers.

Fig. 11). Cellulitis of bitten limb

Absence of detectable local swelling 2 hours after a viper bite usually

means that no venom has been injected. However, there are important exceptions to this rule:

3. ECCHYMOSIS:

Discoloration of the skin over the swollen area appears after few hours of bite. It depends on the amount of venom injected and the species which bite. It is one of the sign of severe coagulopathy.

4. BULLAE FORMATION:

In case of Viper bite bullae will appear within 8 hours and it is depending upon the potency and amount of venom injected. If envenomation is moderate, the bullae will be filled with clear, serous fluid. In case severe envenomation with coagulopathy, haemorrhagic bullae will form, it ruptures often and produce ulcers.[35]

Fig. 12).Hemorrhagic and Non- hemorrhagic bullae around the bite mark

5.GANGRENE AND NECROSIS:

Bites on the digits and in areas draining into the tight

fascialcompartments, such as the anterior tibial compartment, are particularly likely to result in necrosis. High intra compartmental pressure may cause ischaemia which contributes, together with direct effects of the venom, to muscle necrosis.

SYSTEMIC MANIFESTATIONS

CIRCULATORY SHOCK

The peptide and protein content of the venom leads to action of kinin system, which is followed by inhibition of bradykinin system.

Shock is one of the leading cause of death in viper bites. It can be either due to hypovolemia from extravasation of blood into the tissue, cardiac abnormalities are due to loss of integrity of the vascular endothelium.

Swollen limb can accommodate many litres of extravasated blood leading of hypovolemic shock, which can take place between 6 to 26 hours after envenomation.

Shock is further worsened by hemolysis with renal and respiratory failure, which can occur early or three to four days after the bite.

HEMOSTATIC ABNORMALITES

Viper is mainly hemotoxic, makinghaemorrhage is the most prominent symptom of systemic envenomation.

Haemorrhagins are the special toxic constituents, present in viper venom out of which aminoacid esterase, specifically activates factor XII, which plays a main role in bleeding due to consumption of coagulation factors as in DIC.

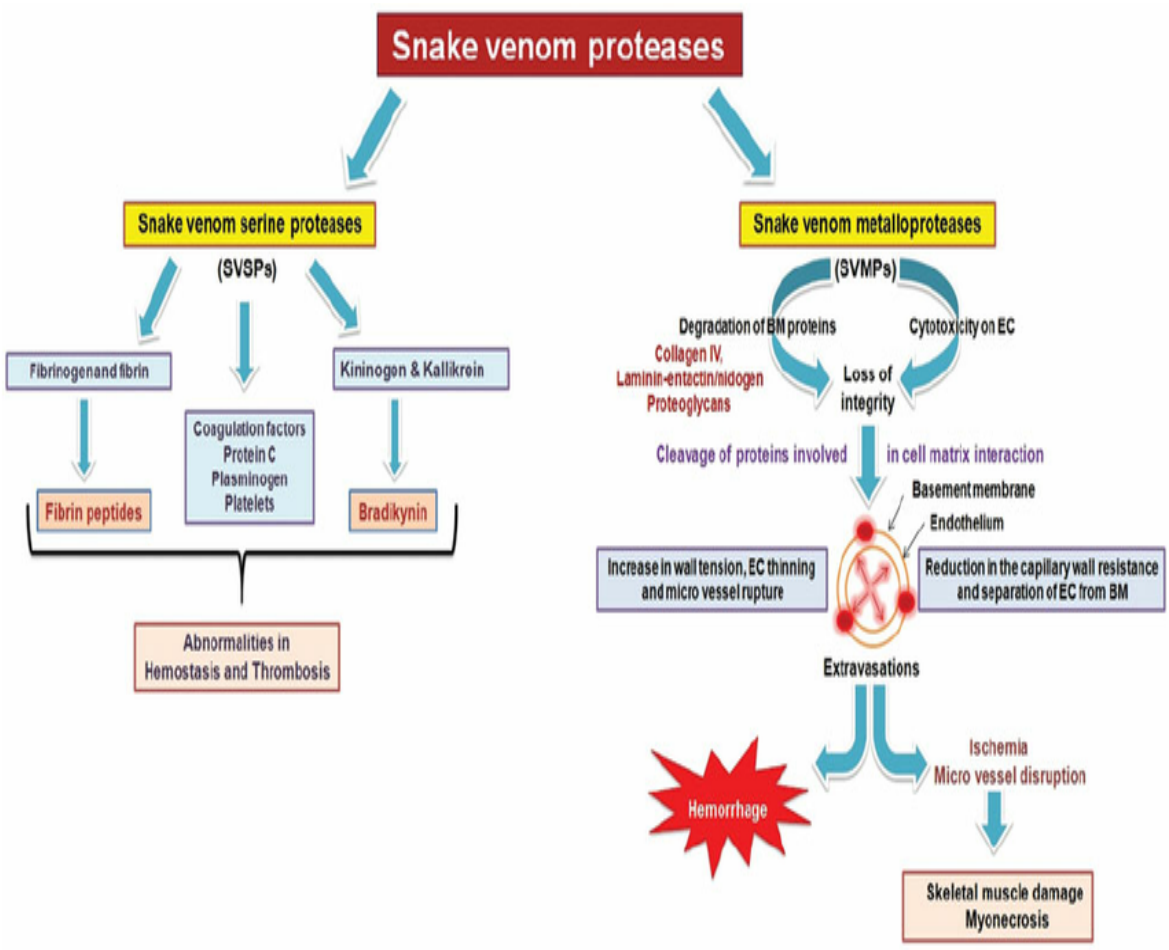


Fig. 13).Hemostatic and neurotoxic mechanisms of snake venom Proteases.

Another mechanism called fibrinogenolysis, has been postulated in the bleeding secondary to Echiscarinatus bites. (V.N.Acharya[36] 1981). R.K. Saini[37]of SMGS Hospital and government medical college, Jammu, who studied 150 cases of viper bites, found that 92% had evidence of primary

fibrinogenolysis whereas only 8% had DIC[37].

Spontaneous systemic haemorrhage is most often detected in the gingival sulci. Blood staining of saliva and sputum usually reflects bleeding gums or epistaxis. True haemoptysis is rare. Haematuria may be detected a few hours after the bite.

Other types of spontaneous bleeding are Ecchymoses, intracranial and subconjuctivalhaemorrhages, bleeding into the floor of the mouth, tympanic membrane and gastrointestinal and genitourinary tracts, petechiae and larger discoid and follicular haemorrhages.

Bleeding into the anterior pituitary (resembling Sheehan's syndrome) may complicate envenoming by Russell's vipers. Persistent bleeding (>10 minutes) from the fang puncture wounds and from new injuries such as venepuncture sites and old partially healed wounds is the first clinical evidence of consumption coagulopathy.

Formation of haemorrhagic blebs with uncontrolled bleeding from the site of bite, is the earliest sign of haematotoxicity in viper bites.

Patients present with ecchymosis, purpura and hematoma within 2 – 24 hours of bite :Schwartzman like phenomenon

The most common symptoms of hematotoxityisHematuria (microscopic or frank) followed by Hemetemesis, Malena, Gum bleed, Hemoptysis. Cerebral haemorrhage can also occur[4].

Mortality usually occurs due to shock and haemorrhage. Acute renal

failure can occur due to occlusion of renal vasculature by micro thrombi, shock and hypovolemia. Intravascular hemolysis manifests as hemoglobinemia and hemoglobinuria[45].

Peripheral smear showing fragmented erythrocytes, is an indication of microangiopathichemolysis associated with severe anemia and acute renal failure.

CARDIOVASCULAR MANIFESTATIONS:

Viper bite leads to disturbances in victim, collapse, hypotension, shock, pulmonary edema, chemosis, arrhythmias.

NEUROLOGICAL MANIFESTAIONS:

Drowsiness, alteration in olfaction, ptosis, external opthalmoplegia, facial muscle paralysis, nasal twang of voice, aphonia, nasal regurgitation, dysphagia, respiratory paralysis, acute flaccid paralysis are the common neurological manifestations[4].

Viperid neurotoxicity is usually attributed to venom phospholipase A2 , it is a feature of envenoming by Crotalusdurissusterrificus, small south African bitis species, and Indian and srilankanRussells viper's (DusotaRussellis). Paralysis descends on with elapid envenoming and progresses to bullae and respiratory muscles.

Rhabdomyolysis manifests as generalized myalgia and muscle tenderness.

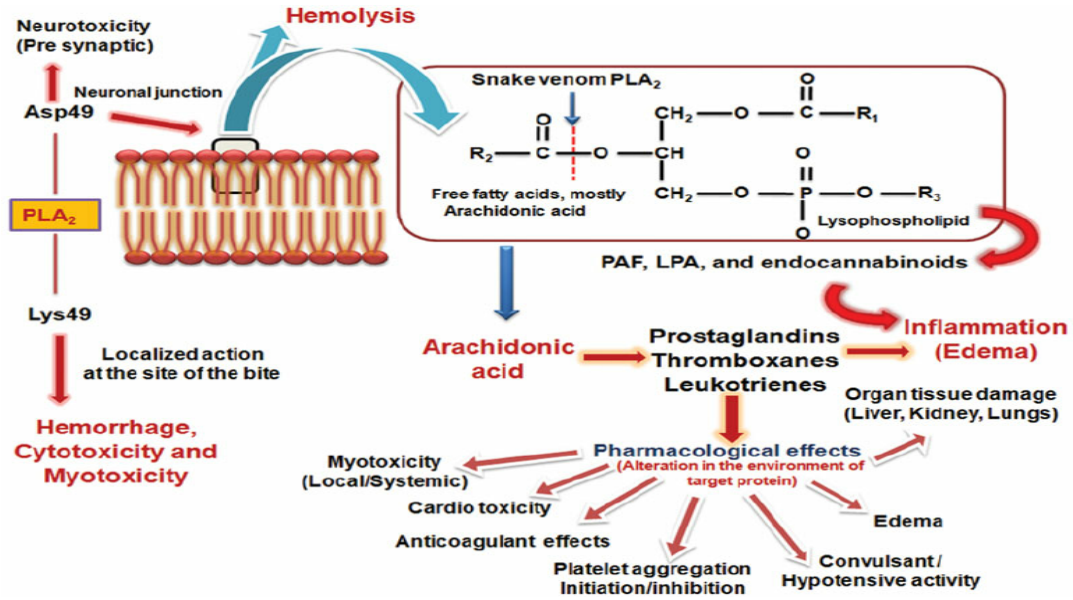


Fig. 14).Various toxic manifestations of snake venom and their mechanisms

ELAPID ENVENOMATION

Most of the victims develop no local effects but develop neurotoxic features like ptosis, opthalmoplegia, respiratory paralysis etc.

LOCAL SIGNS OF ENVENOMATION:

- Krait usually does not produces local envenomation effect.
- Severe local burning pain is a presenting feature of a cobra bite.
- Because of the direct cytolytic action of cobra venom, local necrosis in cobra bite occurs.
- But in King cobra (Ophiophagus Hannah) bite, local necrosis is minimal but in results in swelling of the limb and formation of bullae.

NEUROTOXIC SYMPTOMS:

- The first symptom of systemic envenomation is repeated vomiting
- Earliest sign of neurotoxicity is drowsiness which occurs between 15 mins to 5 hours of envenomation
- But the most common and earliest manifestation is bilateral ptosis
- Patients experience difficulty in vision, double vision, immobility of the eyeball
- These eye signs are of prime importance as they are the only evidence of muscle paralysis in small doses of envenomation
- The other preparalytic signs are blurred vision, paraesthesia, loss of olfactory and gustatory sense, hyperacusis, vertigo , headache and other autonomic symptoms like conjuntival congestion, gooseflesh, increased salivation
- All the above preparalytic signs develop between 1 – 4 hours of bite
- Paralysis is first manifested by ptosis and external opthalmoplegia
- It can either appear early as 15 minutes after the envenomation or a late as 10 hours following the bite
- This is followed by paralysis of facial muscles, tongue, vocal cords, neck muscles and muscles of deglutition which is then followed by dilation of pupils depending on the severity of envenomation.

- According to the severity of envenomation, the symptoms may be insidious in onset or rapid.
- The patient experiences difficulty inn speech, nasal twang due to palatal palsy, difficulty in opening the mouth and swallowing.
- In very severe cases, intercostal muscle paralysis manifests as decreased outward rib movement and by absence of increased intercostal tension.
- The respiration becomes diaphragmatic which is followed by complete paralysis.
- Stupor, shallow breathing, increase in pulse, BP, respiratory rate, cyanoses and increased sweating are the signs of respiratory failure.
- During this stage, patient condition can be worsened by non-reactive pupils, deepening of coma, twitching, convulsions which is then followed by death.
- Limb weakness is the last to develop.
- Proximal muscles are most affected by varying grades of flaccid lim paresis.
- This is followed by a completely flaccid quadriplegia in which deep tendon reflexes are lost.

- The progressive graph of symptoms from early ptosis to terminal respiratory failure is strikingly similar to the course of myasthenia gravis[4].

HEMATOTOXIC SYMPTOMS:

Coagulopathy will usually occur with Asian cobra bite, but not with kraits.The mechanism of coagulopathy is similar to viperid envenomationBut internal bleeding, intravascular hemolysis and acute kidney injury are uncommon with elapid species.

CARDIOTOXIC SYMPTOMS:

These symptoms occurs due to the direct acting cardiotoxins. They are sudden in onset and in severe cases manifests as sweating, cold extremities, hypotension, tachycardia, ST – segment T wave changes which then goes on adownward spiral to hypotension, arrhythmias and cardiac arrest.

MANAGEMENT OF SNAKE-BITE

Steps to be followed in the management of snake bite is as follows

1. **First Aid**
2. **Shift the patient to the nearby hospital**
3. **Resuscitation**
4. **History and Clinical examination**
5. **Investigations**
6. **ASV treatment**
7. **Supportive Management**
8. **Treatment of complications like Respiratory Failure, Acute Kidney Injury**
9. **Treatment for the local wounds**
10. **Rehabilitation**

FIRST AID TREATMENT

It is the initial care given to the patient by others or even by himself. It is very important in the steps of management, as it delays the absorption of venom.

DO'S AND DON'TS IN FIRST AID

- Relieve the anxiety of the patient
- Immobilize the patient either partly or wholly, because on moving the part of body, muscular contraction will increase the absorption

of venom, as superficial lymphatics will carry the venom to systemic circulation.

- "If the necessary equipment and skills are available, consider pressure-immobilization or pressure pad unless an elapid bite can be excluded. In Myanmar, the pressure pad method has proved effective in victims of Russell's viper bite" - (TunPe et al., 1995)[37].
- "Avoid any interference with the bite wound (incisions, rubbing, vigorous cleaning, massage, application of herbs or chemicals) as this may introduce infection, increase absorption of the venom and increase local bleeding" - (Bhat, 1974)[54].

Release of tight bands, bandages and ligatures:

Tourniquets should not be used. If applied, sudden release may cause flushing of venom into the circulation may cause sudden hypotension, severe coagulopathy etc.

" Ideally these should not be released until the patient is under medical care in hospital, resuscitation facilities are available and antivenom treatment has been started" - (Watt et al., 1988)[52].

HARMFUL METHODS OF FIRST AID TREATMENT :

- Incising the bite mark, Hence the blood mixed with venom will bleed out.

- Try to sucking the venom out.
- Applying tourniquets, tight bands just above the bitten area, it was believed that it will obstruct the entry of venom into systemic circulation.
- Giving electric Shock over bite mark.
- Application of chemicals, Plant Juices over bite mark.

Rural people will have strong beliefs on traditional treatments, it should be encouraged as it will cause delay in specific treatment, sometimes it will confuse with local envenoming signs and sometimes in case of coagulopathy, continuous bleeding may occur from incised wounds.

Fig. 15). Tourniquet was applied in right lower limb above bitten area

TIGHT (ARTERIAL) TOURNIQUETS ARE NOT RECOMMENDED!

"MOST TRADITIONAL FIRST AID METHODS SHOULD BE DISCOURAGED : THEY DO MORE HARM THAN GOOD !"[4]

TRANSPORT TO HOSPITAL :

- The victim should be transported to nearby Government Hospital or healthcare facility immediately.
- He can be shifted by using motor vehicles, bicycle,train in resting position, if possible should be transported by using Ambulance.

INITIAL RESUSCITATION :

After receiving the patient, he should resuscitated as all medical emergency,

"ABCDE APPROACH"

1. "**A**irway patency
2. **B**reathing (respiratory movements
3. **C**irculation (arterial pulse)
4. **D**isability of the nervous system (level of consciousness)
5. **E**xposure and environmental control (protect from cold, risk of drowning etc.)[4]

HISTORY AND PHYSICAL EXAMINATION :

History

A short history of the circumstances of the bite and the progression of local and systemic symptoms and signs are very important to assess the severity of envenomation and assume the species if the bitten snake was not identified by the victim.

Four important questions to be asked:

i. "In what part of your body have you been bitten?"

ii. "When and under what circumstances were you bitten?"

iii. "Where is the snake that bit you?"

iv. "How are you feeling now?"

Species identification is important to predict complications, not for treatment. So importance should be given for treatment only. Vomiting and abdominal pain are the earliest symptoms of systemic envenomation. Some patients may develop headache also. History regarding bleeding manifestations and diarrhoea, double vision should be recorded.

"Early clues that a patient has severe envenoming:

- *Snake identified as a very dangerous one.*
- *Rapid early extension of local swelling from the site of the bite.*
- *Early tender enlargement of local lymph nodes, indicating spread of venom in the lymphatic system.*
- *Early systemic symptoms: collapse (hypotension, shock), nausea, vomiting, diarrhoea, severe headache, "heaviness" of the eyelids, inappropriate (pathological) drowsiness or early ptosis/ophthalmoplegia.*
- *Early spontaneous systemic bleeding.*
- *Passage of dark brown/black urine.*[4]*"*

PHYSICAL EXAMINATION :

Physical examination should be done carefully, concentrating both local as well as systemic signs of envenomation.

EXAMINATION OF THE BITTEN PART:

Bite mark :

Venomous snakes will have single fang, usually produce single mark, unless it bitten multiple times, but it is uncommon. Multiple scratch like teeth marks is an important one to differentiate the snake which bite is venoumous or non-venomous, because most of the venomous snakes have single fang. “The presence of isolated fang marks,when related to venomous snake bite,had a sensitivity of 100%, a specificity of 56% and a predictive value of 89%. The finding of multiple scratch like teeth marks had a predictive value of 100%when related to non venomous snake bite[15]” -(Nishiokasde et al 1995)

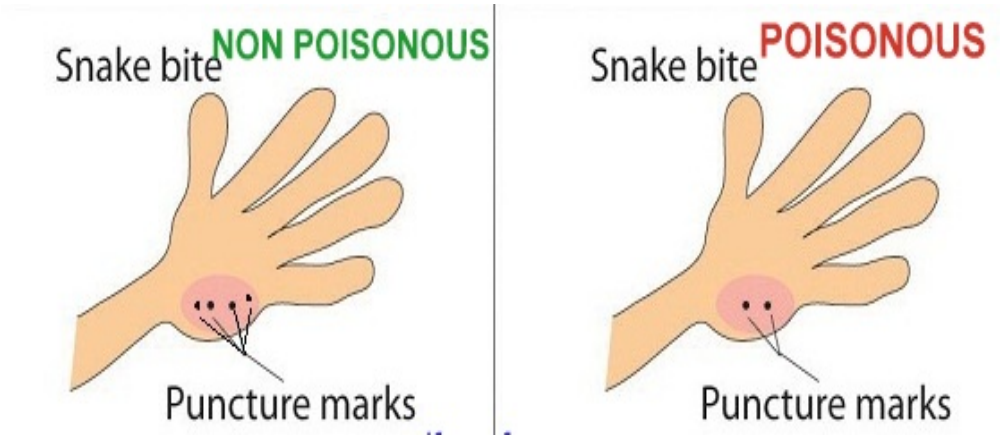


Fig. 16).Bite marks of poisonous and Non poisonous snake bite

Next to bite mark swelling around the bite mark should be assessed.

The extension of swelling, color of skin , presence of bullae, vesicles should be recorded. Extension of swelling should be marked.

The regional lymphnodes should be palpated and tender lymphadenopathy should be recorded.

GENERAL EXAMINATION:

Consciousness and orientation will be impaired in cases of neurotoxic snake bite patients and patients with shock and respiratory paralysis.

Pallor is a indicator of internal bleeding and obscured GI bleeding. Cyanosis may be noted in patients with respiratory failure.

Vital signs such as Blood Pressure, Pulse and Respiratory rate should be recorded. Postural drop in Blood Pressure is recorded, it may be a early sign of Hypovolemia.

Skin all over the body for Petechiae, Ecchymosis, subconjunctival Hemorrhages should examined.

Abdominal tenderness may be due to capillary leak syndrome or internal bleeding. Tenderness over flanks may be due to renal ischemia, occurs in Viper envenomation.

VARIOUS COMPLICATIONS OF SNAKE BITE

Figure 17.1. Neck muscle Weakness.

Figure 17.2. Gum bleeding Due to severe coagulopathy

Figure 17.3 Ecchymosis of bitten limb

Figure 17.4. Cellulitis of dorsum of Hand

NEUROTOXIC ENVENOMING: BULBAR AND RESPIRATORY PARALYSIS

Ptosis, Numbness around mouth are the earlier signs. Extraocular movements should be checked.

Neck muscle weakness is a warning sign of Respiratory paralysis, it should be checked frequently.

Difficulty in Swallowing, nasal regurgitation, nasal twang of speech are signs of bulbar weakness, common in Elapidae envenomation.

Paradoxical respiration – "abdomen expands rather than the chest on attempted inspiration" will occurs due to paralysed inert and subcostal muscles with acting diaphragm.

Single breath count may be used to assess the respiratory muscle weakness, but it become poor valid if patient was anxious.

"Do not assume that snake bitten patients are unconscious or even irreversible "brain dead" just because their eyes are closed, they are unresponsive to painful stimuli, are areflexic, or have fixed dilated pupils.They may just be paralysed![4]"

SUMMARY OF SIGNS AND SYMPTOMS OF SNAKE BITE IN INDIA

Feature	Cobras	Kraits	Russell's Viper	Saw Scaled Viper	Hump Nosed Viper
Local Pain/ Tissue Damage	YES	NO	YES	YES	YES
Ptosis/ Neurological Signs	YES	YES	YES!	NO	NO
Haemostatic abnormalities	NO	NO!	YES	YES	YES
Renal Complications	NO	NO	YES	NO	YES
Response to Neostigmine	YES	NO?	NO?	NO	NO
Response to ASV	YES	YES	YES	YES	NO

Figure 18.Summary of signs and symptoms of snake bite in India

INVESTIGATIONS:

COMPLETE HEMOGRAM

Total and Differential Count : Polymorph nuclear leucocytosis will be present due to acute inflammatory response to snake venom.

Hemoglobin and PCV: Due to extravasation of plasma, initially there is hemoconcentration followed by Anemia due to bleeding or Hemolysis

Platelet Count: Because of the direct effect of the venom or secondary to DIC, thrombocytopenia occurs after bite by ViperaRussellei and EchisCarinatus bites. It is directly proportional to the severity of envenomation in Russell and Saw scaled viper.

Peripheral Smear: Due to Microangiopathichemolysis, fragmented red cells may be present

Plasma / Serum: On account of elevated levels of Hemoglobin and myoglobin in the blood, the plasma may be pink or brown respectively

BIOCHEMICAL ABNORMALITIES

In case of muscle damage, aminotransferases and muscle enzymes are elevated. There is a slight increase in other enzymes picturing mild hepatic dysfunction. Due to extravasation of blood and hemolysis, bilirubin levels are elevated. In the renal failure caused by Russells viper, Hump nosed viper bites and sea snakes bites, potassium, creatinine, urea and BUN levels are raised. Sea snake bites cause extensive rhabdomyolysis, due to

which early hyperkalemia may be seen. In northern Vietnam, krait bites are reported occasionally to cause hypernatremia. In patients with AKI due to snakebites, bicarbonates levels are low as a result of metabolic acidosis.

ARTERIAL BLOOD GASES AND PH:

Neurotoxic envenoming and academia on account of respiratory and metabolic acidosis may lead to asymptomatic respiratory failure.

PULSE OXIMETRY:

It is the earliest non invasive method to monitor respiratory failure and shock

URINE EXAMINATION :

- Color of the urine is tested using dipsticks to detect the presence of blood/ hemoglobin/ myoglobin.
- There is no reliable test to differentiate between the presence of hemoglobin / myoglobin in urine.
- Erythrocytes in the urine can be confirmed by microscopy.
- Presence of red cells casts reflect glomerular bleeding.

In Russell viper bite, earliest sign of increase in capillary permeability and acute kidney injury is massive proteinuria.

TESTS FOR HEMOSTATIC ABNORMALITIES:

20 minute whole blood clotting time (20WBCT) : It is the optimal test

which requires only a single apparatus – a new, clean, dry glass bottle or tube. 2ml of fresh sample of venous blood are placed in the apparatus and left undisturbed for 20 minutes. On tipping the vessel, if the blood is still unclotted, it is indicative of hypofibrinogenemia due to venom induced consumptive coagulopathy. In case of doubt, the test is repeated including a control.

THE PROTHROMBIN TIME:

This test is done to assess extrinsic and common pathway of blood coagulation cascade. It is specific for Russell viper envenomation, but it is not done routinely for snake bite management.An enzyme which initiates coagulation by the direct activation of factor X and does not require the presence of factor VII. Stypen time is the one stage prothrombin time assay performed with Russells viper venom, which can distinguish between deficiency of factor VII and factor X.

PARTIAL THROMBOPLASTIN TIME:

It is a simple procedure to test the intrinsic and common pathways of coagulation but not under routine practice for assessing envenomation

OTHER INVESTIGATIONS:

Electrocardiography:ECG can be used to detect the electrolyte imbalance like hyperkalemia, hypokalemia etc.

USG abdomen and Pelvis: It can be used to picture the morphology of

kidney, corticomedullary differentiation and other signs of capillary leak.

ANTIVENOM TREATMENT:

It is the only specific antidote to snake venom, discovered by Albert Calmatte in 1980 at the institute of Pasteur, in Saigon. The horse or donkey is immunized with venom of one or more species of snakes and the immunoglobulin purified from the plasma of animal is antivenom.

Specific antivenom is one which has been developed against the particular snake, that has bitten the patient henceforth it can be expected to neutralize the particular venom and the venom of closely related species (para specific neutralization).Both monovalent and polyvalent antivenom available of which, polyvalent antivenom is available in India.

In India, Polyvalent antivenom is developed in equines against venom of common krait, spectacled cobra, Saw scaled viper, Russells viper. It is either in liquid form or lyophilized form which can be reconstitute to 10 ml/vial.

ASV manufacturers in India:

- Bharat serum and vaccines, Mumbai.
- Biological E (Evans) limited.
- VINS Bioproducts Ltd.

DOSE: it is calculated according to the average quantity of venom milked out from the snakes captured.

The dose of antivenom needed to neutralize the effects of venom is same in both adults and paediatric age group, since the amount of injected venom is similar.

INDICATIVES FOR ASV:

FEATURES OF SYSTEMIC ENVENOMING:

Abnormalities in Hemostasis: Spontaneous bleeding manifestations**,** Signs of coagulopathy**,**Thrombocytopenia

Signs of NeutrotoxicEnvenoming: Ptosis**,** External Opthalmoplegia**,** Respiratory paralysis**,** Muscle weakness.

Cardiovascular Abnormalities: Hypotension,Circulatory shock**,** Arrythmias**,** ECG changes.

Acute Kidney Injury Manifestations: Oliguria**,** Elevated blood urea nitrogen and serum creatinine levels**,** Signs of metabolic acidosis**,** Changes in the color of urine.

Signs Of Hemolysis And Rhabdomyolysis: Muscle aches and pain (clinically)**,** Hyperkalemia (laboratory).

LOCAL ENVENOMING

- Locall swelling involving more than half of the bitten limb within 48 hours
- Rapid extension of welling within a few hours of bite
- Development of an enlarged tender lymph nodes.

- Antivenom treatment can be given even if the patient presents with signs of systemic envenoming after several days or with hemostatic abnormalities after 2 or more weeks since it can reverse the signs of envenoming.

CONTRAINDICATIONS TO ANTIVENOM

There is no absolute contraindication to antivenom treatment. People with history of allergic reaction to snake venom and those with a strong history of atopic diseases are at higher risk. Hence they should be administered with antivenom only in case of systemic envenoming

ADMINISTRATION OF INJ. ASV

Freeze dried form is reconstituted with 10ml of sterile water per vial which is administered via the intravenous route either by the intravenous push injection or intravenous infusion.Local administration is usually not recommended.

Intravenous push injection: It is an economical method in which the antivenom is given by slow intravenous infusion

Intravenous infusion: The antivenom is diluted in approximately 10 ml of normal saline or distilled water.

The patient must be in observation for at least 1hr so that early anaphylaxis can be detected and treated with epinephrine.

RESPONSE TO ANTIVENOM

General signs: Nausea, headache, generalized pain resolving rather quickly which may be partly due to placebo effect.Spontaneous bleeding manifestations resolves within 15-30 minutes. Hemostatic integrity (assessed by 20WBCT) is usually normal within 3-9 hrs.

Hemodynamic status: in patient in shock, blood pressure rises within the first 30-60 minutes.

Changes In Urine Colour: urine returns to its normal colour since active hemolysis and rhabdomyolysis may resolve within few hours.

Neurotoxic envenoming: In case of post synaptic type, signs usually takes several hours, but it may also improve as early as 30 mins, which is not same as in the case of presynaptic toxins.

RECURRENCE OF SYSTEMIC ENVENOMING:

Systemic envenoming may recur within 24 – 48 hours after an initial response to antivenom. This may be due to as a result of improved blood supply following correction of hemodynamic abnormalities, there may be absorption of venom from the site of bite. Redistribution of venom into the vascular space.Indications for repeating the initial dose of ASV.Persistence or recurrence of hemostatic abnormality after 6 hours.Bleeding after 1 – 2 hours.Worsening neurotoxic and cardiovascular signs

ASV REACTIONS:

Hypersensitivity reactions: (10 mins – 3 hours)

Within 10 mins – 3hours of administration of antivenom, patient develops itching commonly present over the scalp and urticaria, fever, nausea, vomiting, drycough, diarrhoea, abdominal colic and tachycardia.In a few cases, the patient may go in for life threatening anaphylaxis, bronchospasm, angioedema, hypotension. They are not true allergic reaction because there has been no evidence of specific IgE. They are mostly due to complement activation by IgG aggregate or due to direct stimulation of mast cells by antivenom proteins

Pyogenic reactions: (within 1 – 2 hours)

Patient develops rigors, fever, decline in blood pressure and vasodilation which are due to contamination of ASV by pyogens during the manufacture

Late (serum sickness type) reactions: (after 2 – 12 days)

Patient presents with features of fever, nausea, itching, recurrent urticaria, arthralgia, myalgia, lymphadenopathy, vomiting, diarrhea, periarticular swellings, mononeuritis multiplex proteinuria which leads to immune complex nephritis and very rarely, the patient may present with encephalopathy.

TREATMENT OF ANTIVENOM REACTIONS:

Early anaphylactic Reaction:

Epinephrine : It is the drug of choice.

Dose : 0.5 mg deep intramuscular or Subcutaneous. In case of coagulopathy slow IV injection with 1 :10000 dilution can be given.

ChlorPheniramine Maleate :

It is antihistaminic, should be given immediately after Inj.Epinephrine.

Dose :10 mg for adults, 0.2 mg/kg for Children.

Steroids : It is given to prevent late reactions of Type 1 hypersensitivity.

Hydrocortisone – short and rapidly acting steroid, dose is 100 mg for adult, 2mg/kg for Children.

Pyogenic Reactions : Patient must be treated with tepid sponging and antipyretics.

Late Serum Sickness Reaction: It can be treated with a 5 – day course of oral histamines. In case of no response within 24 – 48 hours, patient should be treated with 5 day course of oral prednisolone.

TREATMENT OF THE BITTEN PART :

The cellulitis should be treated with antibiotics, Serratiopeptidases, analgesics and proper Limb elevation. NSAIDS should be avoided, as it may cause renal damages. If it is massive, have signs of compartmental syndrome, fasciotomy should be done after correcting coagulopathy.

SYNDROMIC APPROACH TO SNAKE BITE ENVENOMATION.

It is controversial now, because the clinical signs and symptoms of snake bite envenomation was studied thoroughly with so many research and it is not practiced now because of availability of polyvalent antisnake venom.Eg: Some elapid snakes like Asian cobra will cause severe local envenomation, may be confused with viper envenomation. In India Russell's viper venom sometimes causes both local severe envenomation with neurotoxic signs like ptosis, it may be mistakenly taken as Cobra bite Envenomation. "Syndromic approach" may be useful, when the bitten snake has not been identified and only monospecificantivenoms are available and also for statistical purposes.

SYNDROMIC APPROACH TO SNAKE BITE ENVENOMATION

Syndrome 1

Local envenoming (swelling etc.) with bleeding/clotting disturbances = **Viperidae (all species)**

Syndrome 2

Local envenoming (swelling etc.) with bleeding/clotting disturbances, shock or acute kidney injury **= Russell's viper (hump-nosed pit viper in Sri Lanka and SW India)**

with conjunctival oedema (chemosis) and acute pituitary insufficiency **= Russell's viper, Myanmar**

with ptosis, external ophthalmoplegia, facial paralysis etc and dark brown urine **= Russell's viper, Sri Lanka and South India**

Syndrome 3

Local envenoming (swelling etc.) with paralysis **= cobra or king cobra**

Syndrome 4

Paralysis with minimal or no local envenoming
Bitten on land while sleeping on the ground **= krait**
Bitten in the sea, estuary and some freshwater lakes **= sea snake**

Syndrome 5

Paralysis with dark brown urine and acute kidney injury:

Bitten on land (with bleeding/clotting disturbance) **= Russell's viper, Sri Lanka or South India**

Bitten on land while sleeping indoors **= krait *(B. niger, B. candidus, B. multicinctus)*, Bangladesh, Thailand**

Bitten in sea, estuary and some freshwater lakes (no bleeding/clotting disturbances) **= sea snake**

Figure 19.Syndromic approach to snake bite envenomation

SPECIES IDENTIFICATION

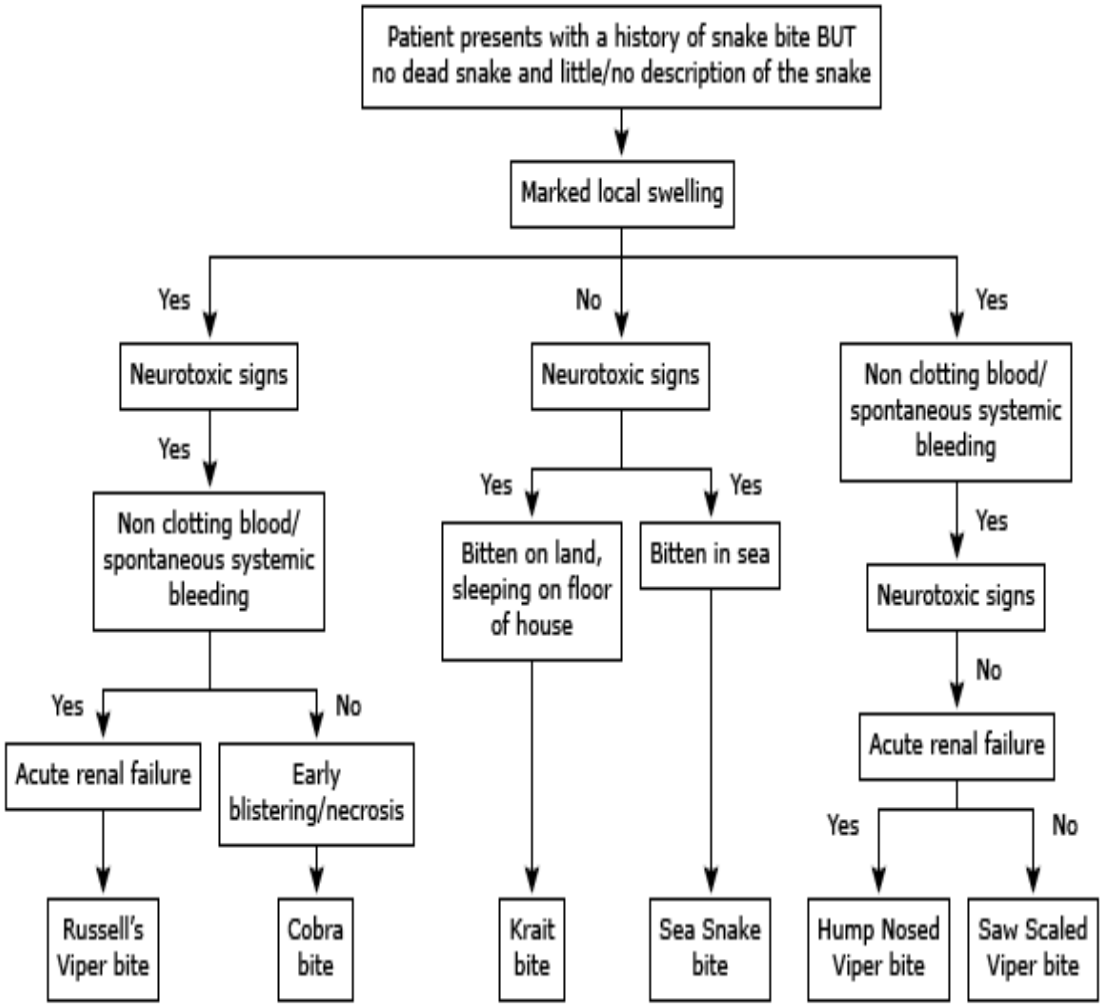


Figure 20. Species identification

ACUTE KIDNEY INJURY IN SNAKE BITE

This is most common in victims of Russell's viper and some species of *Bothrops* will develop acute injury within hours of bite. Pre Renal as well as Renal injury will occur in snake bite envenomation.

ANATOMY OF KIDNEYS

DEFINITION: kidneys are the pair of organs situated in the retro peritoneum. Its main function is to remove the excess water and salts and to remove the waste products of metabolism.

EXTERNALLY – kidney is bean shaped. It has

- 2 poles – the upper pole which is broad and is related to the suprarenal gland and the other, lower pole is narrow
- 2 borders – lateral border is concave and medial border is convex, through which hilum passes through
- Hilum – a depression in the medial border gives rise to the hilum through which the structures passes from anterior to posteriorly are the renal vein, renal artery and renal pelvis
- Location – occupies upper border of T_{12} to middle of $L_{3.}$ In the epigastric, hypochondriac, lumbar and umbilical quadrants. Right kidney is slightly lower than the left
- Shape – bean shaped
- Size – 11*6*3 cm

- Weight – 150 g in males and 135 g in females

COVERINGS OF KIDNEY

- Fibrous capsule – It is the thin membranous layer covering the kidney which can be easily stripped off
- Perirenal Or PerinephricFat : Next to fibrous capsule there is a layer of adipose tissue that constitute the perinephric fat, that are more in the borders. It has two layers, anteriorly fascia of Gerota and posteriorly, fascia of Zuckerkandal. It is a single multilaminated structure that divides at variable point to cover the structures
- Pararenal Fascia : It consist of fat in varying quantities more in the lower poles and posterior surface
- Importance Of Renal Fascia : Its forms the support for the kidneys. If this fat is lost in conditions like extreme fasting, it leads to 'kinking of ureters"

STRUCTURE

In coronal section, the kidney shows the outer reddish brown cortex, the inner pale medulla and the space called the renal sinus. Renal medulla forms conical masses called the pyramids, apices form the renal papillae. Renal cortex is formed of cortical arches and the renal columns. The space that extends into the kidney from hilum called the renal sinus. It contains branches of renal artery, renal vein tributaries and renal pelvis.

BLOOD SUPPLY

Arterial supply by renal artery is a branch of abdominal aorta**.**

Renal artery divides to anterior and posterior division, which gives rise to segmental artery, then to interlobar arteries, which in turn gives rise to arcuate artery, this arcuate artery divides to interlobular arteries which are end arteries

MULTIPLE FUNCTIONS OF KIDNEYS

The main function of kidneys are the excretion of waste products of metabolism namely urea, from aminoacid metabolism. Creatinine from the muscle creatinine, bilirubin from hemoglobin, they also help in removing the toxins from the foreign chemicals, drugs, hormonal metabolites

It helps in the regulation of water and electrolyte balance, by formation of urine, Glomerular filtration**,** Tubular reabsorption**,** Tubular secretion.

- Kidneys play an important role in maintaining acid base balance, since only the kidneys excrete few acids like sulphuric acid from the protein metabolism.
- It maintains the arterial pressure by the rennin angiotensin system
- In production of erythrocytes, by the secretion of hormone called erythropoietin, which stimulates the bonemarrow in production of RBCS, the main stimuli is hypoxia.

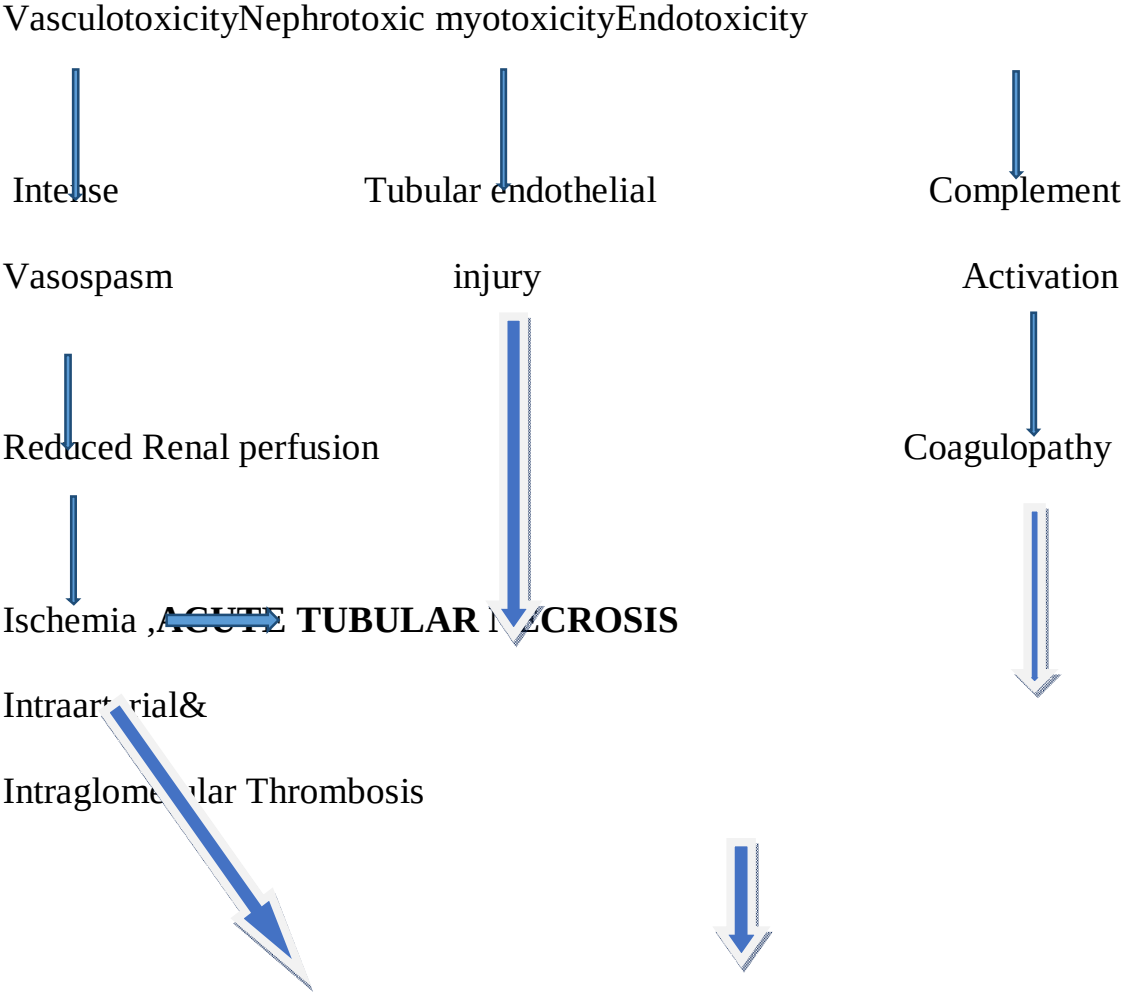
PRE RENAL CAUSES FOR ACUTE KIDNEY INJURY :

- IntravasculsarHypovolemiadue to recurrent vomiting, Fluid restriction practiced as a custom in Rural Tamilnadu, accumulation of fluid in the bitten limb as massive cellulitis may cause reduced plasma flow to Kidney resulted in treatable Pre-AKI.
- Capillary Leak Syndrome- due increased vascular permeability secondary to systemic envenomation may cause third space fluid collection and intravascular hypovolemia.
- Hypovolemia should be corrected with IV crystalloids like Normal Saline and Ringer's Lactate. Central Venous Pressure should be monitored, maintained 7-10 cm of water.
- Sometimes allergic reactions with Antisnake venom, Anaphylaxis may cause kidney injury.

Direct renal injury

Direct renal injury will occur due to following reasons : Toxic products released from intra vascular haemolysis, direct toxicity by venom, disseminated intra Vascular Coagulation, Capillary leak syndrome, Papillary necrosis and drug induced interstitial nephritis. Patients bitten by Russell's vipers may become oliguric within a few hours of the bite. Loin pain and tenderness may be experienced within the first 24 hours and, in 3 or 4 days, the patient may become irritable and hypertensive and may

convulse and become comatose with evidence of metabolic acidosis.



FLOW CHART : MECHANISM OF RENAL INJURY IN SNAKE BITE

RENAL PATHOLOGY :

I. Acute tubular necrosis is the commonest lesion associated with good prognosis.

II. Cortical necrosis may be patchy or diffuse. The renal cortical necrosis is due to the Schwartzman-like phenomenon[24]. In diffuse cortical necrosis renal failure is irreversible and patient needs renal

replacement therapy. In patchy cortical necrosis patient may continue in chronic renalfailure.

III. Papillary necrosis has been reported from Calicut. Patients may complain of passing tissues in the urine and is associated with colic andhaematuria[36].

IV. Tubulo – Intestinalnephritis.

- Late in onset (after 7 days)
- Non – Oliguric renal failure detected by biochemicalmonitoring
- May be due to ASV or other drugs used in themanagement
- Good prognosis.

V. Hemorrhagic Glomeruonephritis is very rare.

WARNING SIGNS OF ACUTE KIDNEY INJURY

a) Dwindling or no urine output

b) Rising blood urea/creatinine concentrations

c) Clinical "**URAEMIA SYNDROME**":

- Nausea, vomiting,
- Hiccups, fetor,
- Drowsiness, confusion, coma,
- Flapping tremor, muscle twitching, convulsions
- Pericardial friction rub,

- Signs of fluid overload.

STAGING OF ACUTE KIDNEY INJURY:

RIFLE AND AKIN STAGING:

In 2004, RIFLE – Risk, Injury, Failure and End stage renal disease criteria was formed and it defined acute kidney injury based on Serum Creatinine, Urine output and GFR.

Due to some limitations like need for baseline creatinine, Difficulty in calculating GFR, in 2007, Acute Kidney Injury Network (AKIN) was formed and it was used to define and categorise Acute Renal Injury into three groups with hourly urine output with serum creatinine. It can be used for AKI of All causes.

RIFLE	RISK	INJURY	FAILURE
CREATININE	INCREASED X 1.5	INCREASED X 2	INCREASED X 2 OR ≥ 4 MG/DL
GFR	DECREASED > 25%	DECREASED >50%	DECREASED >75%
URINE OUTPUT	<0.5ML/KG/H X 6H	<0.5ML/KG/H X 12H	<0.3ML/KG/H X 24H OR ANURIA X 12H
AKIN	**STAGE 1**	**STAGE 2**	**STAGE 3**
CREATININE	INCREASED X 1.5 OR ≥ 0.3 MG/DL	INCREASED X 2	INCREASED X 2
URINE OUTPUT	<0.5ML/KG/H X 6H	<0.5ML/KG/H X 12H	<0.3ML/KG/H X 24H OR ANURIA

Fig. 21). AKIN and RIFLE criteria

MANAGEMENT OF AKI :

Most of the patients with acute renal failure are oliguric, defined as "urineoutput of less than 400 ml/day or less than 20 ml/hour[4]".

Conservative management may be avoided for these patients, the chance for need of dialysis is increased in this patients.

If the patient has signs of intravascular volume depletion, indicated by supine or postural hypotension, or empty neck veins, severe dehydration should be proceeded as follows

A. Establish intravenous access.

B. Insert a urethral catheter with full sterile precautions

C. Fluid challenge[4]:

- Two litres of isotonic saline over one hour is to be given or the fluids to be given until the jugular venous pressure/ central venous pressure has risen to 8-10 cm above the sternal angle (with the patient propped up at 45º).
- The patient should be closely observed while this is being done.
- The fluid challenge should be stopped immediately if pulmonary oedema develops.
- If the urine output does not improve it is reasonable to try a Furosamide and/or mannitol challenge, but these are not of proven benefit.

D. **Furosemide (frusemide) challenge:** 100 mg of furosemide is injected slowly (4-5 mg/minute). If this does not induce a urine output of 40 ml/hour, give a second dose of furosemide of 200 mg. If urine output does not improve, try conservative management[4].

E. Conservative management:

- If the urine output is not improving, despite these challenges, no further diuretics should be given and fluid intake should be restricted to a total of the previous day's output plus "insensible losses" (500-1000 ml/day).
- The patient should be referred to a renal unit.
- The diet should be bland, high on calories (1700/day), low in protein (less than 40g/day), low in potassium (avoid fruit, fruit juices and potassium-containing drugs) and low in salt.
- Infections will cause tissue breakdown and increase urea levels. They should be prevented or treated promptly with non-nephrotoxic antibiotics (i.e. avoid aminoglycosides such as gentamicin)[13].

F. **Biochemical monitoring:** Serum potassium, urea, creatinine and, if possible, pH, bicarbonate, calcium and phosphate should be monitored frequently.

G. Management of complications :

1. **Metabolic acidosis :** If the patient is hypotensive and profoundly acidotic (deep sighing "Kussmaul" respirations, very low plasma

bicarbonate concentration or very low pH - <7.10), sodium bicarbonate should be given. It should be based on volume of distribution of bicarbonate which is 50% of body weight, bicarbonate deficit can be calculated.

2. **Hyperkalemia:** Plasma potassium should be monitored. Hyperkalemia should be managed promptly according to the severity with calcium gluconate, Beta agonists, Insulin with Dextrose infusion, potassium binders etc[53].

3. **Dialysis :**

Indications for Dialysis :

- Clinical uraemia
- Fluid overload
- Blood biochemistry-one or more of the following
- Potassium >7 mmol/l (or hyperkalaemic ECG changes)
- Symptomatic acidosis

Prevention of renal damage in patients with Myoglobinuria or Haemoglobinuria :

- It is done to minimize the risk of renal damage from excreted myoglobin and/or Haemoglobin.

- Correction of hypovolaemia and maintain saline diuresis (if possible)
- Correction of severe acidosis with bicarbonate.
- Mannitol infusion :Give a single infusion of mannitol (200 ml of 20% solution over 20 minutes)(not of proven benefit)

Management of Diuretic phase of kidney injury

This is as important and as life-threatening as the oliguric phase. Urine output increases to 5-10 litres/24 hours following the period of anuria. The patient may become polyuric and volume depleted so that salt and water must be carefully replaced. Hypokalaemia may develop, in which case a diet rich in potassium (fruit and fruit juices) is recommended.

Management of Renal recovery phase :

The diuretic phase may last for months after Russell's viper bite. In Myanmar and South India, hypopituitarism may complicate recovery of Russell's viper bite victims. Corticosteroid, fluid and electrolyte replacement may be needed in these patients.

Persisting renal dysfunction:

Persistent tubular degenerative changes were observed in patients with Russell's viper bite, who will be continuing to have albuminuria, hypertension and nocturia for up to 11 months after the bite, despite apparent recovery in renal function.

In India, 20%-25% of patients referred to renal units with acute renal failure following Russell's viper bite suffered oliguria for more than four weeks suggesting the possibility of bilateral renal cortical necrosis. This can be confirmed by renal biopsy or contrast enhanced CT scans of the kidneys, non invasive CT-KUB is better than Renal biopsy.

Patients with patchy cortical necrosis show delayed and partial recovery of renal function but those with diffuse cortical necrosis require regular maintenance dialysis and eventual renal transplantation.

METHODOLOGY

This study was done at Govt. Mohan Kumaramangalam Medical college hospital, Salem during a period betweenApril 2015 to March 2016.This is a Prospective and observational study which had a sample size of 100 patients

SOURCE OF DATA

The study group included 100 patients admitted to GMKMC Salem with history of snake bite and who satisfied inclusion and exclusion criteria.

METHOD OF COLLECTION OF DATA

Patients were evaluated by taking a detailed history, clinical examination and laboratory investigations. A proforma was specially designed for data collection including all these.

INCLUSION CRITERIA

1.History of Snake bite with signs of Envenomation

2. Progressive elevation of serum creatinine>0.3mg/dl from baseline, a percentage increase in the serum creatinine concentration of >50% or oliguria of less than 0.5ml/kg/hr for more than 6hrs.

3. Age is more than 18 years.

EXCLUSION CRITERIA

1.Patients with Pre existing Renal Diseases with history of Snake bite.

2. Extreme age groups - age more than 80 years

3.Patients with contracted kidneys with normal Renal Parameters with history of Snake bite.

All patients were subjected to the following investigations

- Hb,
- PCV
- Platelets
- Urine complete
- Blood Urea, Serum creatinine,
- USG abdomen & Pelvis
- ECG

PROCEDURE IN DETAIL :

Patients admitted in Emergency Room, GMKMCH with history of Snake bite were taken into the study. Some of the patients were initially treated in some hospitals and referred to our hospital with Acute Kidney injury also taken. Details regarding initial treatment, renal parameters have been collected.

Acute kidney injury was defined according to AKIN criteria. Patients were classified into 4 groups- NO AKI, AKIN 1, AKIN 2, AKIN 3 by monitoring urine output Hourly and Serum Creatinine. Patients were followed up from admission to discharge. If patients developed acute kidney injury means, they were transferred to

Nephrology ward and continuous monitoring was done. CBC- Hb, PCV, and Platelet count was monitored daily. Renal parameters monitored twice daily. Patients were followed up till discharge.

STATISICAL ANALYSIS

The study design was a prospective non interventional observational study. All data collected were noted using a structured proforma, including the investigations. Data was analysed using statistical package and SPSS structured software to find out the proportion of acute kidney injury among 100 patients, and their clinical profile and outcome of them.

FUNDING AGENCY: None.

ETHICAL CONCERNS: As per the institution protocol.

CONSENT: Informed consent was taken as per standard procedure that is followed in the institution.

RESULTS AND OBSERVATIONS

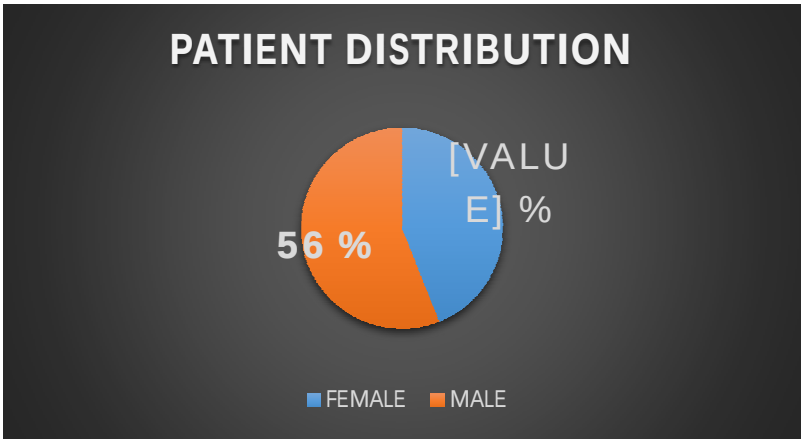
OBSERVATIONS & RESULTS

The study was prospective, observational, non- interventional and follow up study. 100 patients were selected randomly who fulfils the criteria for the study. Following parameters were observed in our study.

1).GENDER WISE DISTRIBUTION OF PATIENTS

Gender	No. Of patients	Percentage
Male	56	56 %
Female	44	44%

Table .2.Gender wise distribution of patients



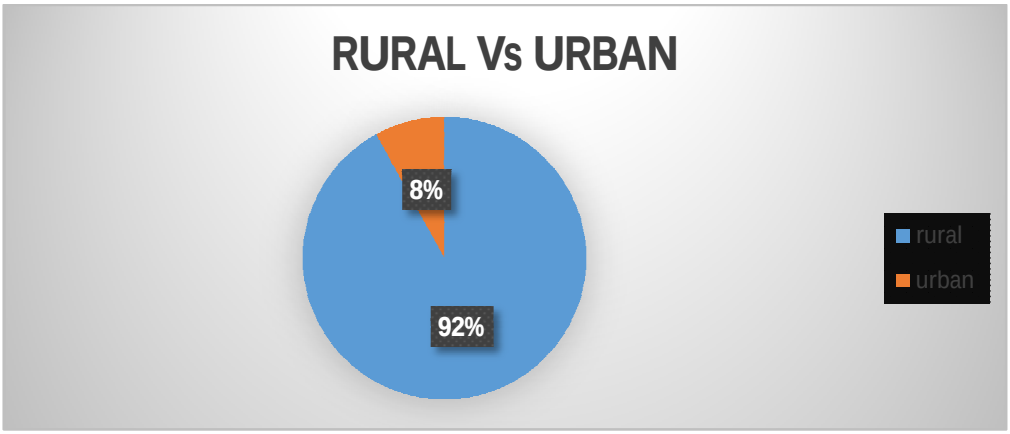
22. GENDER WISE DISTRIBUTION OF PATIENTS

In total number of patients observed in our study is 100. Among them 56 patients are male and 44 patients are female. Most of the patients from rural areas of Salem district and nearby districts – Namakkal, Erode, Dharmapuri, Krishnagiri, Villupuram and Trichy.

1.GENDER WISE TABLE WITH RURAL AND URBAN PATIENTS.

Gender	Rural	Urban
Male	50	6
Female	42	2
Total	92	8

Table 3).Gender wise table with rural and urban patients.



23).GENDER WISE TABLE WITH RURAL AND URBAN PATIENTS.

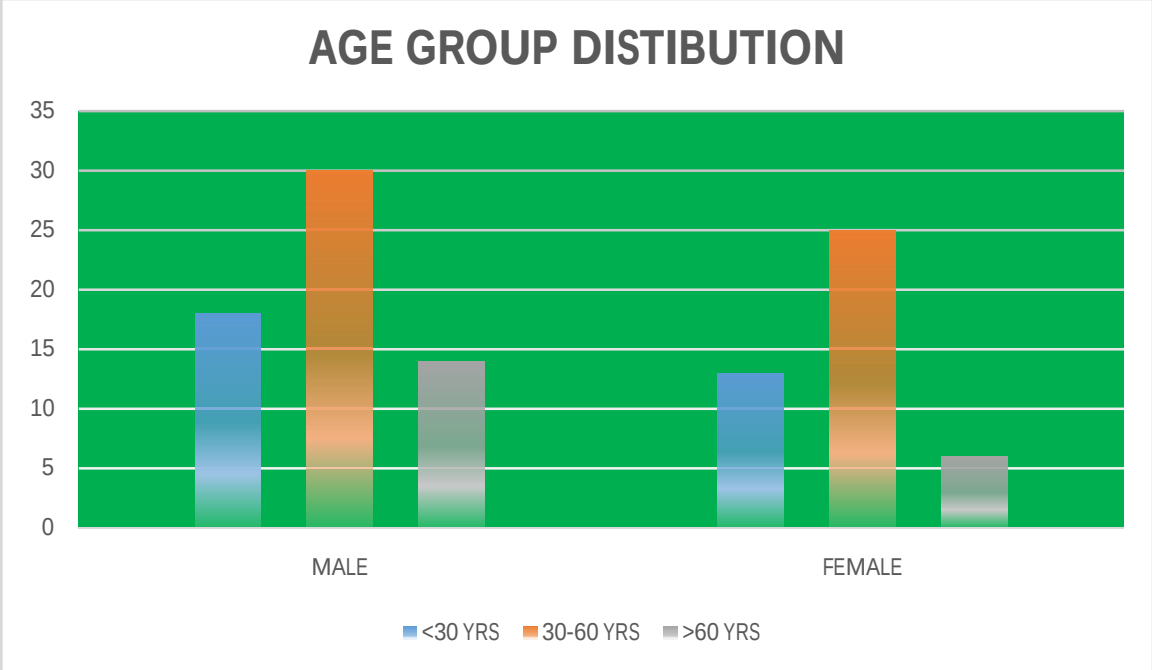
Most of the patients from rural areas, all are related to agriculture as farmers, relatives of agricultural workers, field workers etc. Both male and female patients were almost equal in our study.

In patients from urban areas, they have been exposed to snake while travelling or roadside, or living in slum areas etc. Among 8 patients from urban area, 5 were male and 3 were female. They reached the hospital within 1hr and the outcome was good

3). AGE GROUP DISTRIBUTION WITH GENDER

Gender	<30 years	30-60 years	>60 years
Male	18	30	8
Female	13	25	6
Total	31	55	14

Table no. 4). Age group distribution with gender



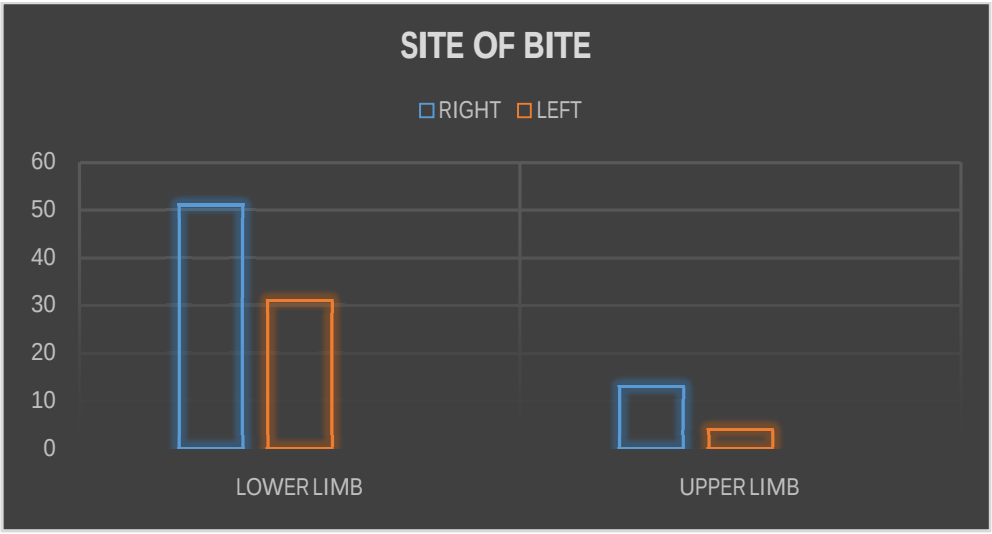
24). AGE GROUP DISTRIBUTION WITH GENDER

Most of the patient in both sex groups are in between 30-60 years, only few patients are in more than 60 years of age. Most of the patients do not have any co-morbidities. Mean age is 41 years with minimum age of 18 years and maximum age of 80 years

4). SITE OF BITE WITH GENDER

Site of bite	Right	Left	Total
Foot	51	32	83
Hand	13	4	17

Table no.5). Site of bite with gender



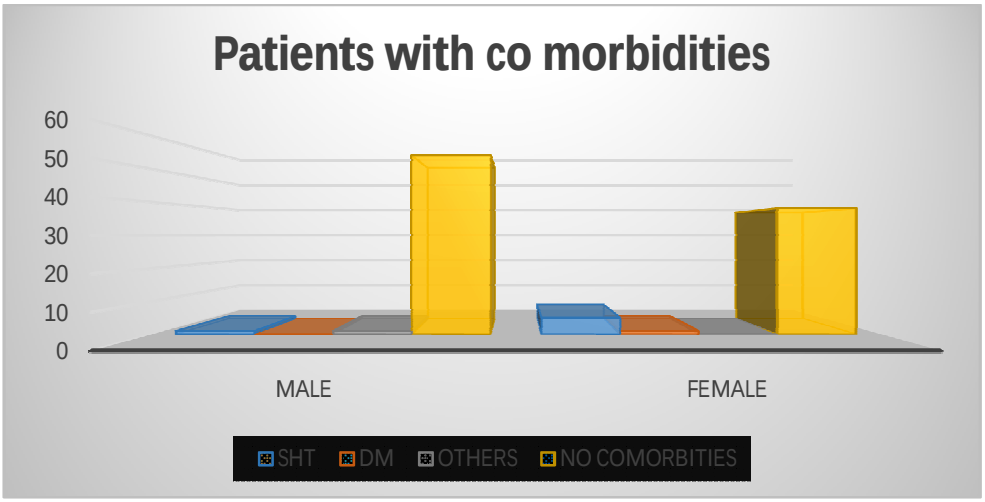
25). SITE OF BITE WITH GENDER

Right lower limb is the commonest site of bite in both sex groups. Bite in the hand occurred in patients working in the field particularly agricultural workers. Some of the patients had been bitten over shoulder, thigh and one patient had been bitten over the face. As most of them are field workers, bare foot walkers, dorsum of foot and ankle were the most common areas of bite.

5). PATIENTS WITH CO MORBIDITIES :

GENDER	SHT	DM	OTHERS
Male	1	0	1
Female	5	1	0
Total	6	1	1

Table no.6).Patients with co morbidities.



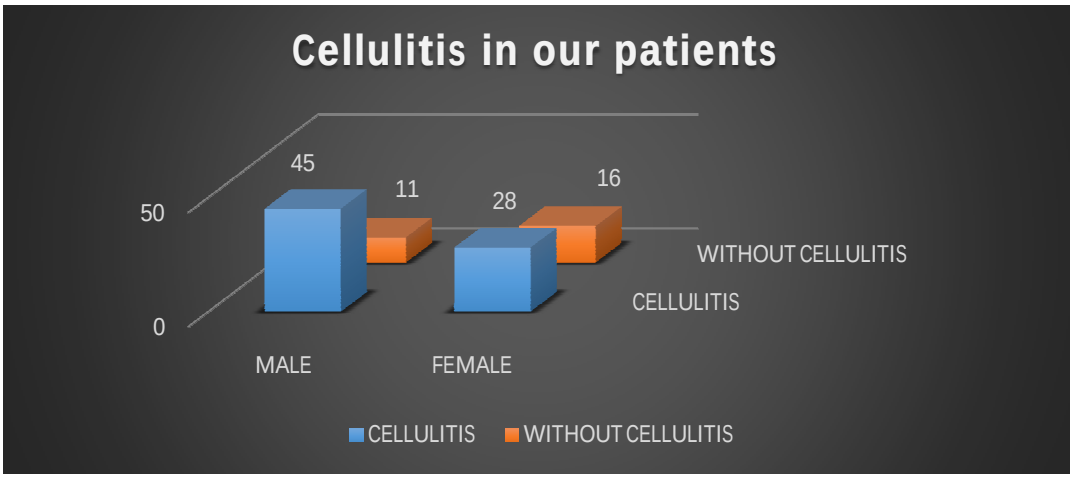
26). PATIENTS WITH CO MORBIDITIES.

Most of the patients in our study do not have any co-morbidities. 92% of patients in our study were not having any co-morbidities. One patients was HIV positive, not on art. One patient was both hypertensive and diabetic. 5 patients are hypertensives on regular anti-hypertensive drugs and hypertension was under control.

6). CELLULITIS IN OUR PATIENTS.

Gender	Cellulitis	Without cellulitis
Male	45	11
Female	28	16
Total	73	27

Table no.7).Cellulitis in our patients.



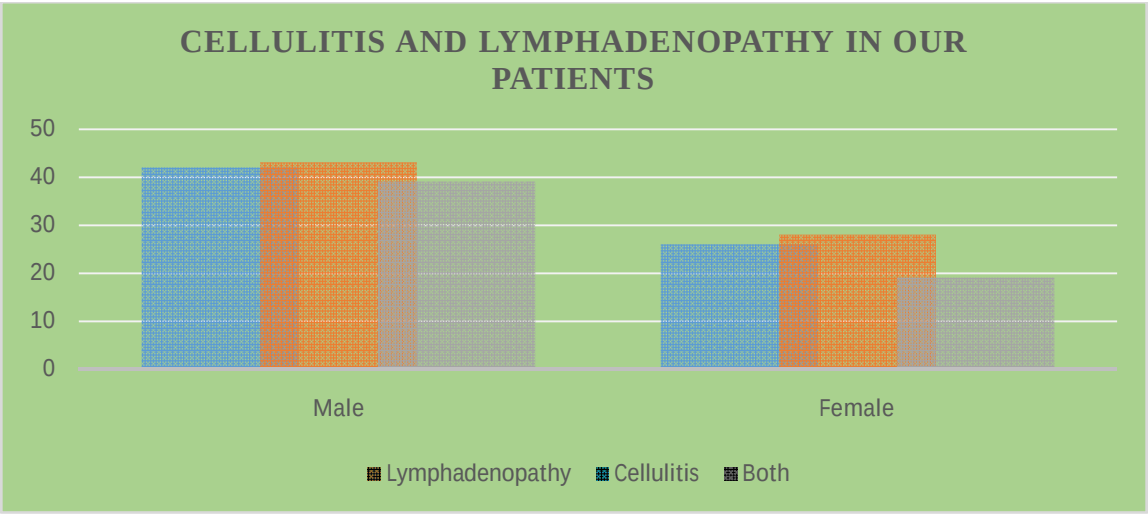
27). GENDER WISE CELLULITIS DISTRIBUTION

Cellulitis is more common with male, corresponds to 62 % in total cellulitis. In my study 56 male patients were admitted, among them 45 (80%) patients developed cellulitis. In female patients 28/44 which is 64%. Development of cellulitis is depend upon the species of snake bites, and potency of the venom and not depends upon the limbs. But progression of cellulitis is depends upon the effective treatment given.

7).REGIONAL LYMPHADENOPATHY AND CELLULITIS IN RELATION TO GENDER:

Gender	Lymphadenopathy	Cellulitis	Both
Male	42	45	39
Female	26	28	19
Total	68	73	58

Table no. 8).Regional lymphadenopathy and cellulitis in relation to gender



28).REGIONAL LYMPHADENOPATHY AND CELLULITIS IN RELATION TO GENDER:

Cellulitis is sign of local envenomation of some snake species, occurred more in males (45/56 =80%) than females (28/44=64%). Lymhadenopathy is also more common in male patients (42/56 =75%) compared with (26/44 =59%). Both of them are signs of local envenomation, both was present in 39 male patients and 19 female patients. Hence most of the patients are having both cellulitis and lymphadenopathy in our study.

8).RELATION OF BITE- TO NEEDLE TIME WITH ACUTE KIDNEY INJURY:

Bite to needle time	**NO AKI**	**AKIN 1**	**AKIN 2**	**AKIN 3**	**Total**	**Chi square**	**P**
< 6 hrs	52	11	4	17	84	15.166 Df- 2	0.0005
6 – 12 hrs	4	1	2	4	11		
>12 hrs	0	0	1	4	5		

Table No. 9) : Bite to needle time in relation to AKIN staging

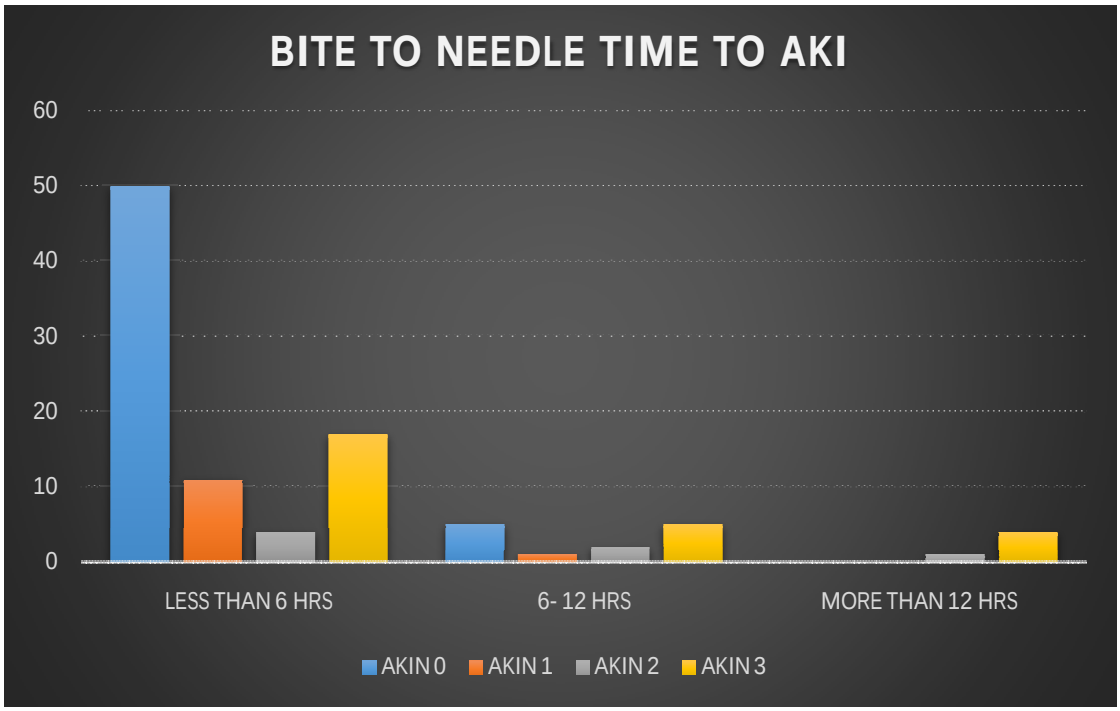
AKIN staging	**Bite to needle time**												**Total**	**Chi square**	**P**
	<1 hr		**1-2 hrs**		**2-3 hrs**		**3-4 hrs**		**4-5 hrs**		**5-6 hrs**				
	N	%	N	%	N	%	N	%	N	%	N	%			
NO AKI	19	38	17	31	9	18	3	6	2	4	0	0	50	18.329 Df-15	0.045
AKIN1	4	36	3	28	2	18	2	18	0	0	0	0	11		
AKIN2	0	0	2	50	2	50	0	0	0	0	0	0	4		

AKIN3	5	31	6	38	1	6	1	6	2	13	2	6	16		
Total	28	34	28	34	14	18	6	7	4	5	2	2	82		

Table No.10). Bite to needle time (less than 6 hours) related to AKIN staging.

82 patients were admitted in hospital before 6 hours, among them 50 patients did not develop AKI. 11 patients developed AKIN 1 and 4 patients developed AKIN 2 and 17 patients developed akin 3. Among patients admitted before 6 hours, 28 patients admitted immediately within one hour, among them 19 didn't develop AKI, but 5 people developed akin 3. In 6-12 hours group, 5 people didn't develop AKI, but 5 peoples developed akin3. In more than 12 hours group, all developed severe AKI. Among 5 people, 4 developed stage 3 AKI and one developed stage 2 AKI.

So early admission sometimes may not prevent development of AKI. But delay in admission is definitely resulted in bad prognosis, sometimes death may occur in those patients.

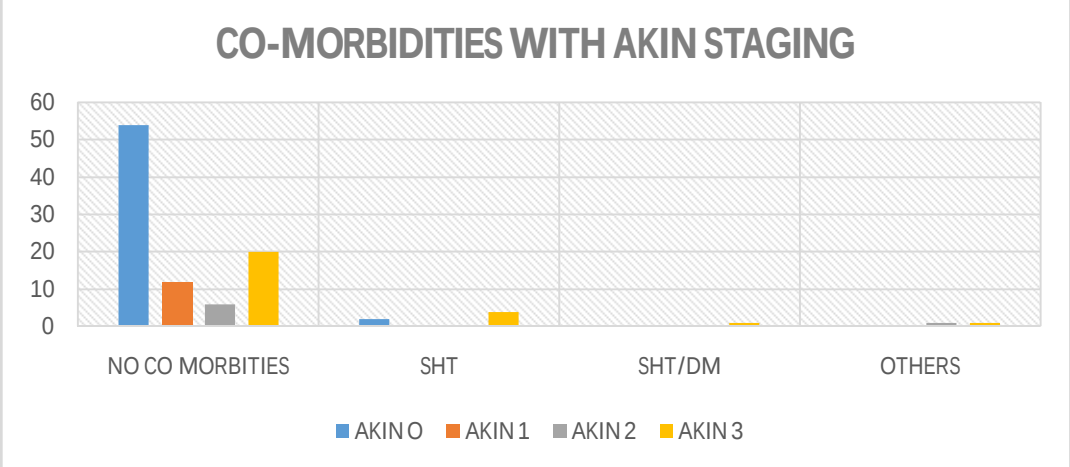


29).BITE TO NEEDLE TIME IN RELATION TO AKIN STAGING

9).CO MORBIDITIES OF PATIENTS RELATED TO STAGING OF AKI

Comorbidities	NO AKI	AKIN 1	AKIN 2	AKIN 3	Total	Chi square test	P value
Without co morbidities	54	12	6	20	92	22.767 Df-9	0.007
SHT	2	0	0	4	6		
SHT/DM	0	0	0	1	1		
Others	0	0	1	0	1		

Table no. 11).Co morbidities of patients related to staging of AKI



30).CO MORBIDITIES OF PATIENTS RELATED TO STAGING OF AKI

Most of the patients in our study were not having any co morbidities. 8 patients had comorbidities like SHT,DM. It plays an important role in development of AKI. Among 8 patients, 6 patients

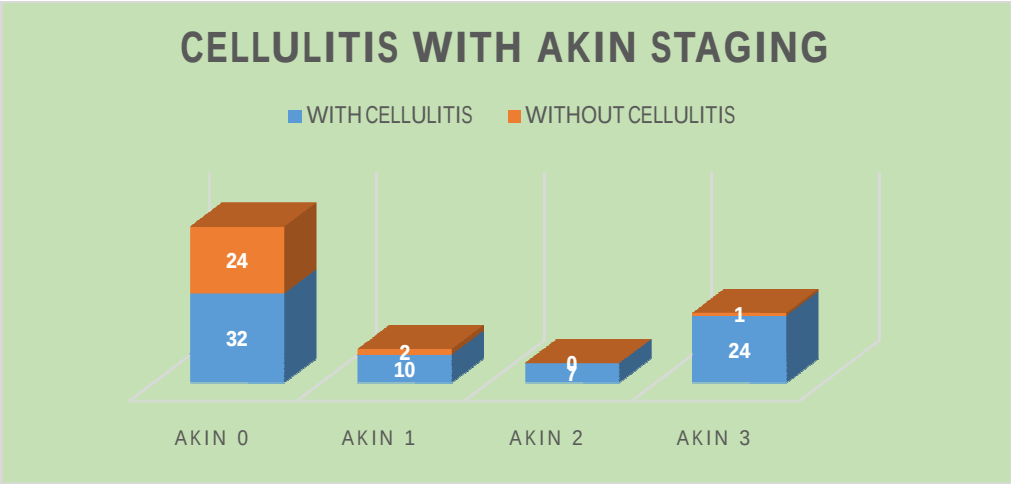
developed severe AKI. Eventhough patients with co-morbidities were only few in number, significant association is noted.

10).CELLULITIS IN PATIENTS RELATED TO STAGING OF AKI :

Cellulitis	**NO AKI**	**AKIN 1**	**AKIN 2**	**AKIN 3**	**Total**	**Chi square tests**	**P value**
With cellulitis	32	10	7	24	73	7.097 Df-2	0.028
Without cellulitis	24	2	0	1	27		

Table No. 12).Cellulitis in patients related to staging of AKI

Among 56 patients in no AKI group, 32 patients (58%) had cellulitis and 24 patients (42%) didn't have cellulitis. 25 patients in akin3 group, only one patient (4%) didn't have cellulitis. This association is significant as p value is <0.05. AKI can be expected in patients with severe cellulitis. Accumulation of litres of fluid into the bitten limb as cellulitis may be one of the reason for pre-renal AKI in this group.



31).CELLULITIS IN PATIENTS RELATED TO STAGING OF AKI

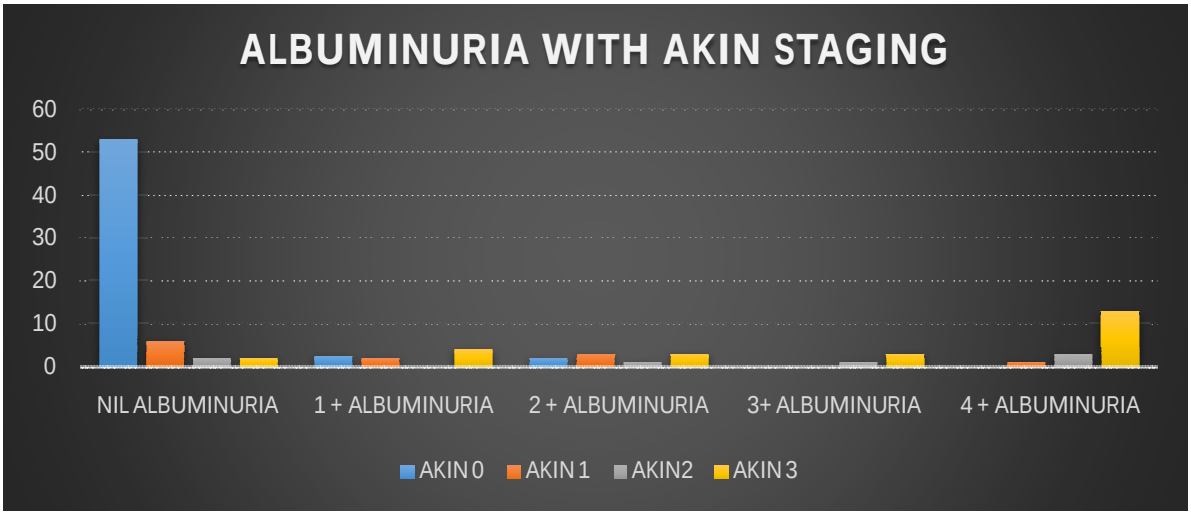
11.PROTEINURIA WITH AKIN STAGING :

Albuminuria	NO AKI	AKIN 1	AKIN 2	AKIN 3	Total	**Chi square test**	P value
0	53	6	2	2	63	74.807	0.000
1	1	2	0	4	7	Df-12	
2	2	3	1	3	9		
3	0	0	1	3	4		
4	0	1	3	13	17		

Table no.13). Proteinuria with AKIN staging

Proteinuria is a sign of renal injury. It was occurred in 37 % of patients. 3 % of patients without AKI also developed proteinuria. But in most of the AKI patients, proteinuria is bad sign of outcome. 4+ proteinuria was

present in 13 patients and 2 patients did not have proteinuria. It is one of the early predictor of AKI and prognosis. If heavy proteinuria is present, renal injury also is more.

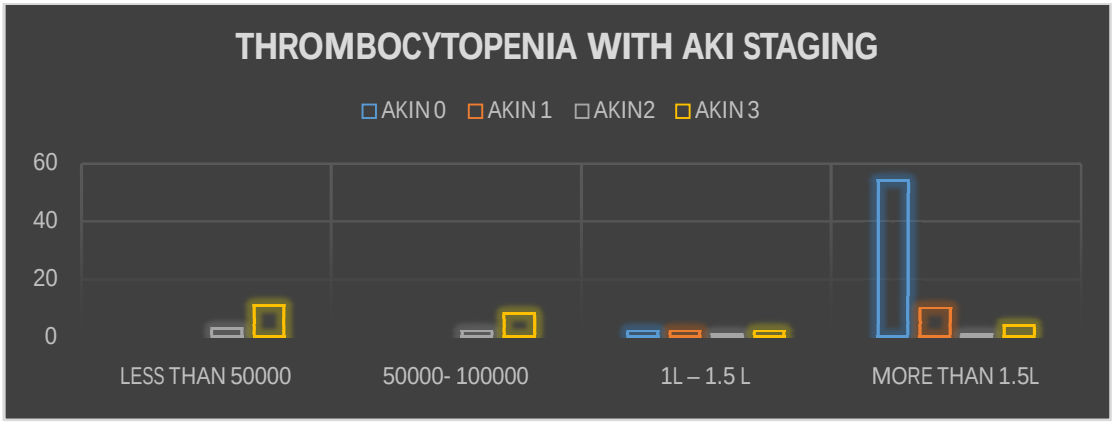


32)..PROTEINURIA WITH AKIN STAGING

12.THROMBOCYTOPENIA WITH AKIN STAGING

PLC	AKIN 0	AKIN 1	AKIN2	AKIN 3	Chi square test	P value
<0.5L	0	0	3	11	73.856 Df-9	000
0.5 – 1 L	0	0	2	8		
1– 1.5 L	2	2	1	2		
>1.5L	54	10	1	4		

Table no.14).Thrombocytopenia with AKIN staging



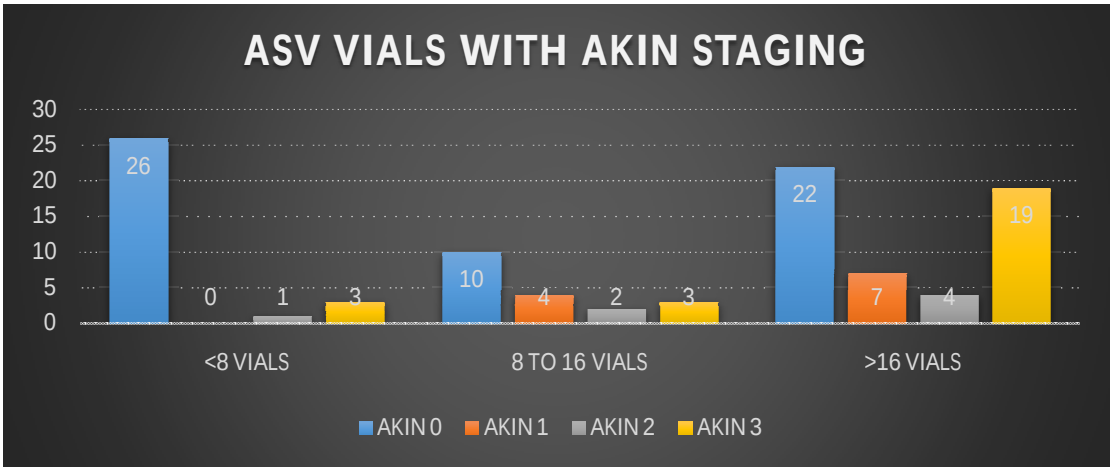
33).THROMBOCYTOPENIA WITH AKIN STAGING

Thrombocytopenia was present in almost all patients with AKI. In AKIN 0 group, only 2 patients had mild thrombocytopenia in the range of 1 – 1.5 lakh/mm3. In AKIN 3 group, 21/25 patients (84%) had thrombocytopenia, among them 44% of patients had very severe thrombocytopenia. In AKIN stage 2, very severe thrombocytopenia was occurred in 3 patients among 8 patients. Hence thrombocytopenia canbetaken as a marker to predict severity of AKI. Also thrombocytopenia is directly proportional to severity of AKI in our study.

13).AKIN STAGING IN RELATION TO NUMBER OF VIALS REQUIRED TO NEUTRALISE VENOM(CLINICALLY):

ASV Vials	NO AKI	AKIN 1	AKIN 2	AKIN 3	Total	Chi square test	P value
<8	25	0	1	3	29	19.127	0.0039
8-16	10	4	2	3	19	Df-6	5
>16	22	7	4	19	52		

Table no. 15). No. Of ASV vials required to neutralise Venom Clinically



34).AKIN STAGING IN RELATION TO NUMBER OF VIALS REQUIRED TO NEUTRALISE VENOM(CLINICALLY):

In patient who required less than 8 vials group, only 4 people(13%) developed AKI. Inj.ASV was not needed to be repeated in these patients. It is sign of mild-moderate envenomation.in patient required to be repeat the ASV of once, 10 patients didn't develop AKI and 9 patients developed AKI. It is a sign of moderate to severe envenomation. In third group, patient required high amount of ASV, 30 patients among 52 means 58% developed severe AKI. Maximum ASV vials given in these patient was 33 vials.

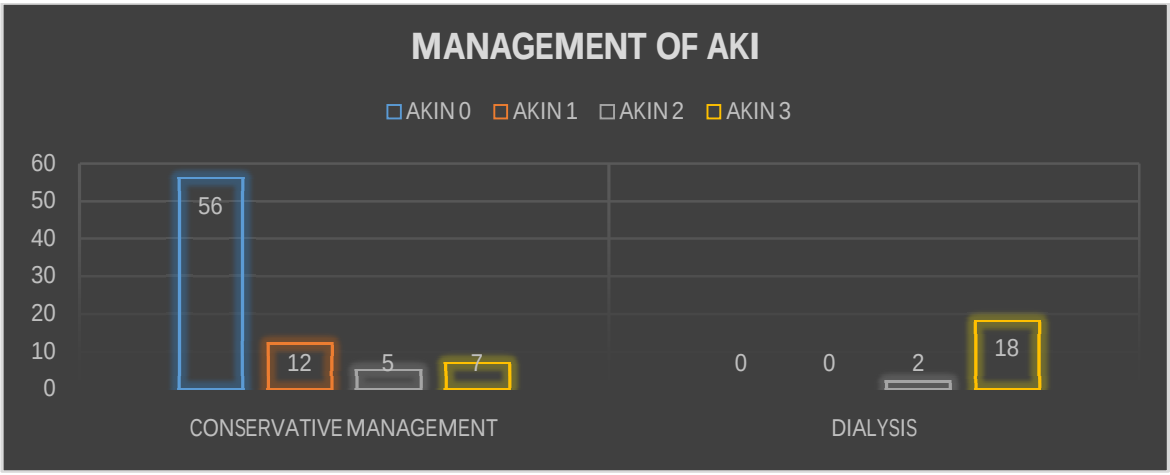
14). MANAGEMENT RELATED TO AKIN STAGING :

Management	NO AKI	AKI N 1	AKI N 2	AKI N 3	Total	**Chi-square tests**	P value

Conservative	56	12	5	7	80	60.926	0.000
Dialysis	0	0	2	18	20	Df-6	
Total	56	12	7	25	100		

Table no.16). Management of AKI in relation to AKIN Staging

In our study among 100 patients, 44 patients developed acute kidney injury. Among them 12 patients are in akin 1 stage and all patients recovered completely without any complications, not required dialysis. 7 patients developed akin stage 2, among them Only one patient required dialysis and that patients also recovered completely. 25 patients developed akin stage 3. Most of the patient, 72% patient required dialysis and some of them died inspite of dialysis and effective management. Late presentation may be one of the reason for worst prognosis.



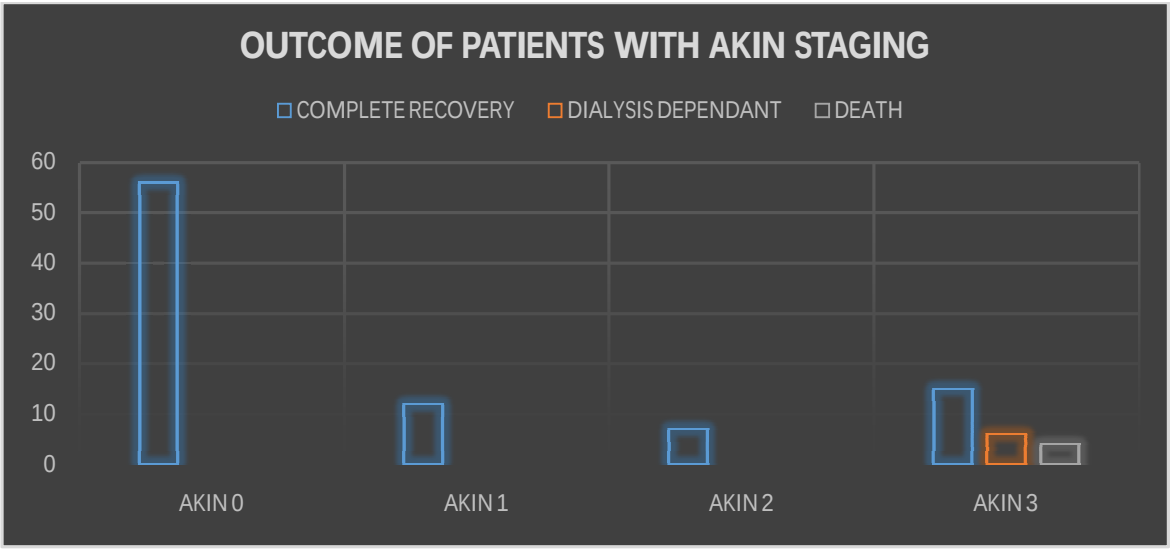
35). MANAGEMENT RELATED TO AKIN STAGING

15.OUTCOME OF PATIENTS WITH AKIN STAGING :

Management	AKIN 0	AKIN 1	AKIN 2	AKIN 3	Total	**Chi-square tests**	P value
Complete recovery	56	12	7	15	90	26.847 Df-6	0.000
Dialysis dependant	0	0	0	6	6		
Death	0	0	0	4	4		

Table no 17). Outcome of patients in various AKIN group

In our study, 44 patients developed AKI. 90 % of patients recovered completely. 12 patients with AKIN 1, 6 patients with AKIN2, 15 patients with akin3 recovered with conservative management. 6 patients become dialysis dependant and 4 patient died, all of them are in stage3 AKIN.



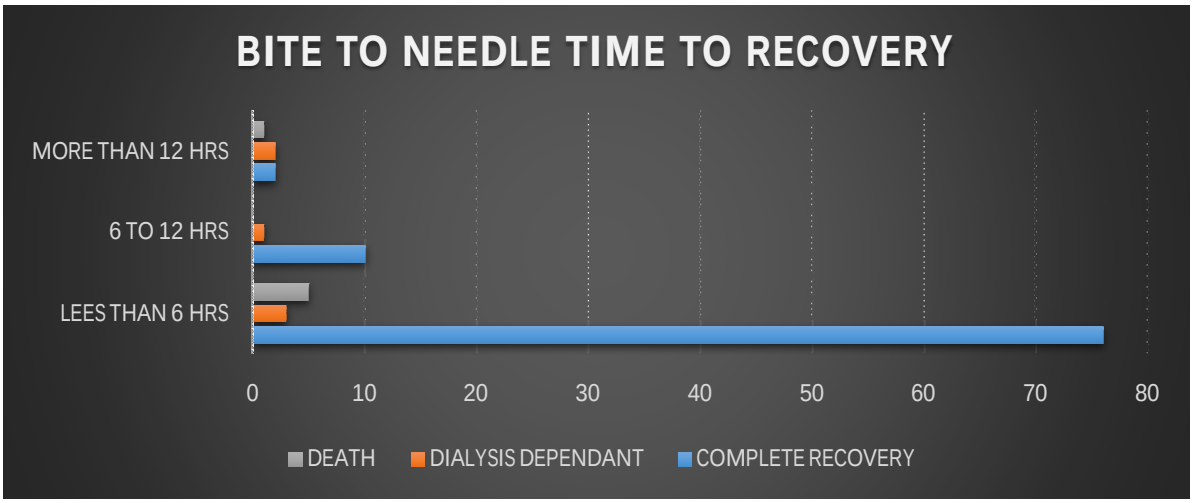
36).OUTCOME RELATED TO AKIN STAGING :

16. BITE TO NEEDLE TIME TO RECOVERY :

Out come	Complete recovery	Dialysis dependant	Death	Chi square test	P value
Lees than 6 hrs	78	3	3	14.306 df -4	0.00637 <0.05
6 to 12 hrs	10	1	0		
More than 12 hrs	2	2	1		
Total	90	6	4		

Table no.18). Recovery of patient in relation to bite to needle time

90 patients in our study recovered completely. Among them 78 patients were admitted before 6 hours, 10 out 11 patients in category 2 admitted in 6 – 12 hours recovered. In more than 12 hours group, 2 patient recovered completely, 2 become dialysis dependant and one patient inspite of dialysis. Biopsy was done in both dialysis dependantpatient. Both the patients developed patchy cortical necrosis.



37). BITE TO NEEDLE TIME TO RECOVERY .

DISCUSSION

DISCUSSION

In our study, 100 patients admitted with poisonous snake bites with features of envenomation. Various parameters were observed and stratified into groups and followed up till discharge.

GENDER VARIATION WITH SNAKE BITE :

In our study, 56 patients were male and 44 patients were female. Male population is more than female since most of the outdoor activities, farming, field works are done by Males usually. In 1992, [14]Hati AK et al, have done one epidemiological survey snake bite in the district of the Burdwan, West Bengal. In that study 54.27% were male patients and 45.23% were female patients.

92% of patients from rural areas of Salem and surrounding districts were admitted. Gender distribution was maintained in that papulation.Only 8% peoples are from urban area.

AGE GROUP DISTRIBUTION :

Most of the patients are in 30 to 60 years of age. Maximum age was taken into my study was 80 years. Most of the patients were young adult patients, active farmers in rural Tamilnadu. To avoid age related changes in the Kidney (GFR changes) extreme age group population was not taken into the study.

In 2006 to 2008, [61]Chattopadhyay et al did a study about snake bite in same

district mentioned above where snake bites are more common. In that study,Patients in the age group of 21-40 years contributed to nearly 60 % of total population and among them 60.47% are male patients.

SNAKE IDENTIFICATION :

Most of the patients (60%) have not identified the snake. Few victims brought the snake to the hospital and most of the patients were not able to differentiate Viper. 5 patients admitted with history of cobra bite with typical features and required ventilator and recovered completely and didn't develop AKI. One patient with krait bite was not taken into the study, because of presence of pre-existing renal disease. Most of the patients had signs and symptoms of Russell Viper bite envenomation.

COMMON SITES OF SNAKE BITE :

Lower limbs are commonest sites of snake bite in our study, particularly Right Lower Limb. Most of them are agricultural workers, used to work with bare foot, used to walk over the grasses. Hence dorsum of foot is the most common site of bite followed lower 1/3 of leg. Bite over the dorsum of hand also common in these patients.Few patients had bite over the thigh, back, shoulder and over the face in one patient, these patients have been bitten while sleeping in the ground.

INCIDENCE OF ACUTE KIDNEY INJURY :

In our study among 100 randomly selected snake bite patients with features of Systemic envenomation, 44 patients developed Acute Kidney

Injury. It is just a proportion of Acute Kidney Injury among 100 patients in our Hospital.

CO-MORBIDITIES IN PATIENTS:

Only few patients were with comorbidities in our study. Among 8 patients, 6 patients had hypertension, one patient had hypertension and diabetes, one patient was HIV positive on Pre-ART. Other co morbidities were not taken into the study.most of the patients (92%) were not having any co morbidities. Among 8 patients, 6 people developed severe Acute Kidney Injury (AKIN2, AKIN3). 4 patients required dialysis and 3 patients become dialysis dependant, because development of patchy cortical necrosis, which was proven by renal biopsy. No death was occurred in these group.

[59]Maulita P Kapadia et al conducted one study regarding acute kidney injury of all causes with co-morbidities. In that study, more than 50% of patients with co-morbidities developed AKI.

CELLULITIS IN RELATION TO DEVELOPMENT OF ACUTE KIDNEY INJURY:

Cellulitis is more common with male, corresponds to 62 % in total cellulitis. In our study 56 male patients were admitted, among them 80% patients developed cellulitis. 64% female patients developed cellulitis.Development of cellulitis is depend upon the species of snake bites, and potency of the venom and not depends upon the limbs. But

progression of cellulitis is depends upon theeffective treatment given. In our study species specific snake bite patients were not taken, so it included pure neurotoxic snake bite patients also.

AKI can be expected in patients with severe cellulitis. Accumulation of litres of fluid into the bitten limb as massive cellulitis may be one of the reason for pre-renal AKI in this group[14].

Rapidly progressive cellulitis one of the indication for repeating the initial dose of Inj.ASV. Secondary bacterial infection, tissue necrosis, compartmental syndrome, vascular occlusion worsen the development of AKI and outcome by releasing inflammatory products and toxins, all damages renal vascular endothelium[60].

Athappan et al : “Regional lymphadenopathy was another significant independent factor for ARF. Just as cellulitis, Regional lymphadenopathy can be a bedside indicator of the amount of toxin released by the snake bite”[9].

CELLULITIS AND LYMPHADENOPATHY RELATED TO ACUTE KIDNEY INJURY:

Both of them are signs of severe local envenomation, both was present in 39 male patients and 19 female patients. Hence most of the patients are having both cellulitis and lymphadenopathy in our study. It is a sign of Viper bite also. 22 /58 (38%) of patients in these group developed stage 3

AKI, with heavy proteinuria, and more than 80% required dialysis and 5 patients become dialysis dependant and 4 patient died of AKI complications. In 2013, [22]Mrudul V Dharod et al done a study and concluded that "92% patients with AKI had moderate to severe cellulitis. On the other hand, only about 55% patients without AKI had moderate to severe cellulitis".

Rapidly progressive cellulitis with lymphadenopathy is one of the early predicting sign of AKI and outcome. It is directly proportional to amount and potency of venom.

PROLONGED COAGULOPATHY WITH ACUTE KIDNEY INJURY:

In our hospital we are following this method to start Inj.ASV and to monitor along with local envenomation signs. In our study, more than 80% had prolonged clotting time and few patients had only local signs of envenomation. In Nearly 20 % , clotting abnormalities were not reversed with In.ASV alone, required blood products like FFP, Whole Blood. Few patients had hematuria, hematemesis and 1 patient had intracerebralhaemorrhage and died.

Acute kidney injury was not developed in patients with normal Clotting time. So it can be taken as risk factor for AKI.

"101 (59.06%) snakebite patients were presented with 20 min WBCT > 20 min and of which 55 (54.45%) patients were suffering from

AKI" - (Jayanta Paul et al)[59].

BITE TO NEEDLE TIME AND DEVELOPMENT OF ACUTE KIDNEY INJURY :

82 patients were admitted in hospital before 6 hours, among them 50 patients did not develop AKI, 11 patients developed AKIN 1 and 4 patients developed AKIN 2 and 17 patients developed AKIN 3.

Among patients admitted before 6 hours, 28 patients admitted immediately within one hour, among them 19 didn't develop AKI, but 5 people developed AKIN 3. In 6-12 hours group, 5 people didn't develop AKI, but 5 peoples developed akin3.

In more than 12 hours group, all developed severe AKI. Among 5 people, 4 developed stage 3 AKI and one developed stage 2 AKI.

In 2012, Jayantapaul et al have done small study in Gujarat, Mean time in between snakebite and administration of ASV (minutes) 110.22 ± 7.60 was observed and mean patients developed acute kidney injury is 66.39 ± 4.36[59].

Suchithra N et al. stated in their study of Snakebite envenoming in Kerala, South India; " Those who received ASV early (bite to needle time < 6hrs) had more severe local envenoming than those who received ASV late (bite to needle time > 6 hrs), but latter group were more likely to suffer complication and those who received ASV late had a higher risk of developing acute renal failure"[48].

Sharma et al.stated that median bite to hospital time was 9 hrs and delayed in admission was more prone to develop acute kidney injury.

Narvencar K et al found that Correlation between early administration of anti snake venom was beneficial in preventing development of acute kidney injury, however severe was the systemic envenomation[46].

" Early administration of antivenom has been demonstrated to completely reverse all clinical manifestations of snake envenomation. But some studies stated that the early administration of Inj.ASV cannot be too strongly emphasized to prevent development of AKI in snakebite patients." – UM.Natarajan et al , SJAMS[42].

So early admission sometimes may not prevent development of AKI. But delay in admission is definitely resulted in bad prognosis, sometimes death may occur in those patients.

THROMBOCYTOPENIA AND ALBUMINURIA WITH AKIN STAGING AND OUTCOME:

Thrombocytopenia & albuminuria was present in almost all patients with AKI.

In AKIN 0 group, only 2 patients had mild thrombocytopenia and in AKIN 3 group, 21/25 patients (84%) had thrombocytopenia, among them 44% of patients had very severe thrombocytopenia. In AKIN stage 2, very severe thrombocytopenia was occurred in 3 patients among 8 patients.

Hence thrombocytopenia can be taken as a marker to predict severity

of AKI. Also thrombocytopenia is directly proportional to severity of AKI in our study. 4+ proteinuria was present in 13 patients, all developed AKIN stage 3, required dialysis and 4 become dialysis de It is one of the early predictor of AKI and prognosis. If heavy proteinuria is present, renal injury also is more.

ASV VIALS REQUIRED TO NEUTRALISE IN RELATION TO AKIN STAGING:

In patient who required less than 8 vials group, only 13% developed AKI. Inj.ASV was not needed to be repeated in these patients, it is sign of mild-moderate envenomation.

In patient required to be repeat the ASV of once, 10 patients didn't develop AKI and 9 patients developed AKI, it is a sign of moderate to severe envenomation.

In third group, patient required high amount of ASV, 30 patients among 52 means 58% developed severe AKI.

Some patients required blood products like FFP, Whole blood in addition to Inj.ASV. Maximum ASV vials given in these patient was 33 vials. All patients required blood products developed AKI.

INTERVENTIONS NEEDED RELATED TO AKIN STAGING :

In our study among 100 patients, 44 patients developed acute kidney injury. Among them 12 patients are in AKIN 1 stage and all patients

recovered completely without any complications, not required dialysis. 7 patients developed AKIN stage 2, among them only one patient required dialysis and that patients also recovered completely. 25 patients developed AKIN stage 3. Most of the patient, 72% patient required dialysis and some of them died in spite of dialysis and effective management. Late presentation may be one of the reason for worst prognosis.

Acute tubule interstitial necrosis is the most common cause acute kidney injury. It will recover completely, if treated promptly. It will recover over the period of 2 weeks. If it was not recovered even after 2 weeks, with oliguria, cortical necrosis should be suspected and it is one of the indication for renal biopsy[12]. Some of the patient with patchy cortical necrosis will recover completely, but they are more prone to develop Chronic Kidney Disease over the period of years.

Diffuse cortical necrosis is having worst prognosis, patient will become dialysis dependant, will require Renal transplant[12].

OUTCOME OF PATIENT :

In our study, 44 patients developed AKI. 90 % of patients recovered completely. 12 patients with AKIN 1, 6 patients with AKIN2, 15 patients with AKIN 3 recovered with conservative management. 6 patients become dialysis dependantfor more than a month and among them 3 developed diffuse cortical necrosis (Biopsy proven) and progressed to chronic Kidney Disease with Dialysis Dependant. 3 patients were discharged with

partial recovery and advised to monitor renal parameters regularly and 4 patient died in hospital, all of them are in stage3 AKIN.

Snake species, seasonal variation, bite to needle time, bleeding complications, and co-morbidities, extend of cellulitis, lymphadenopathy, prolonged clotting time not reversed with ASV alone, hypotension, thrombocytopenia, and proteinuria are plays an important role in the outcome and complications of snake bite envenomation.

Early administration of Inj.ASV, adequate hydration, management of Cellulitis are the important factors for good outcome[9].

CONCLUSION

CONCLUSION

- ✓ Delay in admission to Hospital is strongly correlated with development severe acute kidney injury.
- ✓ Patients with co-morbidities should be monitored carefully, as they are more prone to develop AKI and if develops, outcome is poor.
- ✓ Rapidly progressing massive cellulitis and severe coagulopathy are signs of severe envenomation.
- ✓ Thrombocytopenia and Proteinuria is strongly correlated with poor outcome.
- ✓ Hourly Urine output and serial Renal parameters, ABG should be monitored.
- ✓ AKIN staging can be used for early diagnosis, management, to predict outcome and prognosis.
- ✓ Prompt treatment of snake bite envenomation may prevent development of Acute Kidney Injury in young Healthy Working Population and is a preventable morbidity and mortality.

LIMITATIONS OF THE STUDY

LIMITATIONS OF OUR STUDY

1) Total Number of patients were taken into our study is small and only magnitude of Acute kidney injury occurred among 100 patients was calculated.

2) Incidence was calculated in our study is just a proportion of Acute Kidney Injury among snake bite envenomation patient in our Hospital.

3) Confirmation of species was not done, as most of them were not identified the Snake. Only few people told the name of the Snake.

4) The study was being conducted in a tertiary care centre, many of the patients presented as referred cases with a variety of complications of Snake bite, thereby increasing the number of incidence and major adverse renal outcomes – Berkson's selection bias.

SUMMARY

SUMMARY

This study was conducted in Government Mohan Kumaramangalam Medical College Hospital, Salem with study population 100, with aim to find incidence of acute kidney injury in patients with signs and symptoms of envenomation.

Information regarding circumstances of bite, species of snake, first aid, initial management, delay in reaching the hospital, co-morbidities were collected and vital signs, 20 mins WBCT, Basic Renal Parameters, Complete Hemogram, Urine Routine and thorough examination of local site of envenomation and features of systemic envenomation noted.

Hourly Urine output, 8th hourly renal parameters and daily CBC, Urine Complete were monitored and documented. Patients were classified into 4 groups – NO AKI, AKIN 1, AKIN 2, AKIN 3.

Management was done with adequate IV Fluids, Inj.ASV, Dialysis and treatment of local parts.

All have been documented with a proforma for this study.

Observations and results were analysed. Incidence of acute kidney injury in my study is 44 %. 57% are in stage 3 AKIN and most of them required dialysis. Few became Dialysis Dependant due to Cortical necrosis, most of them are known case of Hypertension.

Case fatality rate in our study is 4 %. All developed stage 3 AKIN. Death was due to complications of Acute Kidney Injury like Acidosis and

one patient died of severe coagulopathy- Intracerebralhaemorrhage.

Early admission into the hospital and administration of Inj.ASV and adequate hydration ,monitoring of renal parameters and coagulation profile by Simple bedside 20mins WBCT may prevent avoidable morbidity and mortality in Healthy, Young Population due to snake bite Envenomation.

ANNEXURES

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PROSPECTIVE STUDY OF INCIDENCE, CLINICAL PROFILE &OUTCOME OF ACUTE KIDNEY INJURY IN PATIENTS WITH SNAKE BITE ENVENOMATION ADMITTED IN GMKMCH

PROFORMA

Name: **IP. No:** **Reg.No :**
Age/sex: **Address:**
D.O.A:D.O.D:

DATE & TIME OF BITE	DATE & TIME OF ADMISSION	DELAY IN ADMISSION (HOURS)
TOURNIQUET APPLIED YES / NO	**SNAKE IDENTIFIED YES / NO**	**IF YES VIPER / COBRA / KRAIT / OTHERS**

COMPLAINTS OF THE PATIENT:
1.Pain at the bite site : Yes / No
2. Bleeding from bite mark : Yes / No
3. Vomiting : Yes / No
PAST HISTORY :H/ O DM / HTN / SEIZURE DISORDER / COPD/ CAD / OTHERS
PERSONAL HISTORY :
DIET : Vegetarian / Non- Vegetarian / Mixed Diet
Smoking :Alcoholism :
TREATMENT HISTORY :
Duration of treatment :
No. Of vials Inj. ASV administered :
Clotting time on Referral :
CLINICAL FEATURES
VITAL SIGNS AT THE TIME OF ADMISSION

BP	PULSE RATE	RESPIRATORY RATE	TEMPERATURE

SIGNS OF TOXICITY

SIGNS	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	TILL DISCHARGE
VITAL SIGNS BP PULSE RATE						
CELLULITIS						

REGIONAL LYMPHADENOPATHY						
CLOTTING TIME						
PTOSIS						
RESPIRATORY PARALYSIS						
SIGNS OF DIC						

SYSTEMIC EXAMINATION:

1. Cardiovascular System :
2.Respiratory system :
3. Per Abdomen :
4. Central Nervous System :

INVESTIGATIONS :

USG KUB :

OTHER INVESTIGATIONS (IF NEEDED) :

PARAMETERS	**DAY 1**	**DAY 2**	**DAY 3**	**DAY 4**	**DAY 5**	**TILL DISCHARGE**
B. UREA						
SERUM CREATININE						
INPUT ~~**OUTPUT(Hrly)**~~						
HB **PLATELET COUNT** **PCV**						
URINE ANALYSIS **PROTEIN** **OTHERS**						
NO. OF VIALS INJ.ASV ADMINISTERED						
ALLERGIC REACTIONS TO INJ.ASV						
TREATMENT: 1.CONSERVATIVE						
2.PERITONEAL DIALYSIS						
3.HEMODIALYSIS						

FINAL INFERENCE: SNAKE BITE WITH ..... TOXICITY WITH/ WITHOUT ACUTE KIDNEY INJURY (AKIN STAGE.....) MANAGED WTH.....

PATIENT CONSENT FORM

STUDY TITLE:

"STUDY ON VITAMIN B12 DEFICIENCY IN CHRONIC METFORMIN THERAPY IN TYPE 2 DIABETES MELLITUS PATIENTS IN GMKMCH SALEM"

DEPARTMENT OF GENERAL MEDICINE, GMKMCH, SALEM.

PARTICIPANT NAME : AGE : SEX:
I.P. NO :

I confirm that I have understood the purpose of investigatory procedure for the above study. I have the opportunity to ask the question and all my questions and doubts have been answered to my satisfaction.

I have been explained about the possible complications that may occur during and after medical/ surgical procedure. I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving any reason.

I understand that investigator, regulatory authorities and the ethics committee will not need my permission to look at my health records both in respect to the current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from the study.

I hereby consent to participate in this studyfor various investigatory procedures and their outcomes.

Time :
Date : **Signature / Thumb Impression Of Patient**
Place :

Patient's name:

Signature of the investigator: _____
Name of the investigator : _____

KEY TO MASTER CHART

A/S	**Age/Sex**
SOB	**Site Of Bite**
BND	**Bite to Needle Time**
COM	**Co-Morbidities**
HTN	**Hypotension**
CEL	**Cellulitis**
RL	**Regional Lymphadenopathy**
WBCT	**Whole Blood Clotting Time**
RF	**Respiratory Failure**
ICR	**Initial Creatinine**
PLC	**Platelet Count**
AKIN	**Acute Kidney Injury Network**
ASV	**ASV Vials**
AR	**Allergic Reactions To ASV**
MX	**Management**
CM	**Conservative Management**

CR	**Complete Recovery**
DD	**Dialysis Dependant**

MASTER CHART

Sl. No.	NAME	A/S	ADDRESS	SOB	BNT	COM	HTN	CEL	RL	WBCT	PTOSIS	RF	ICR	OUTPUT	PLC	PROTENURIA	AKIN	NO OF ASV	AR	MX	OUTCOME
1	Kuppayee	65/F	Thiruchencode	Lt hand	1 hr	No	No	Yes	No	> 20	No	No	2	non-oliguric	160000	Trace	1	24	No	CM	CR
2	Murugesan	45/M	Attur	rt foot	2 hrs	No	Yes	No	No	>20	No	No	2	non-oliguric	240000	Nil	0	16	Yes	CM	CR
3	Lakshmi	65/F	Erode	Rt hand	1 hr	No	No	Yes	No	> 20	No	No	5	oliguric	100000	Trace	3	16	No	Dialysis	DD

4	Muthuramalingam	54/M	Rasipuram	Lt foot	12 hrs	No	No	Yes	Yes	> 20	No	No	1	non-oliguric	195000	Nil	1	16	No	CM	CR
5	Chinnapillai	50/F	Omalur	Rt ankle	8 hrs	No	No	No	No	> 20	No	No	1	non-oliguric	210000	Nil	0	8	No	CM	CR
6	Kuppusamy	70/M	Valapadi	Lt ankle	11/2hr	No	No	NO	NO	>20	No	No	1	non-oliguric	205000	Nil	0	8	No	CM	CR
7	Amutha	20/F	Omalur	Lt ankle	5 hrs	No	No	Yes	No	> 20	No	No	1	non-oliguric	210000	Nil	3	8	No	CM	CR
8	Raman	25/M	Attur	Rt foot	7 days	No	No	No	No	< 20	No	No	3	non-oliguric	80000	Trace	3	5	No	CM	CR
9	Periyasamy	65/M	Chinnasalem	Lt foot	4 1/2hrs	No	No	Yes	Yes	> 20	No	No	1	non-oliguric	55000	Trace	3	30	No	CM	CR
10	Siddan	70/M	Nangavalli	Rt foot	3 hrs	No	No	No	No	>20	No	No	1	non-oliguric	212000	Nil	0	5	No	CM	CR
11	Patchiyammal	37/F	Attur	Lt big toe	1 hr 30 mins	No	No	No	No	> 20	No	No	1	non-oliguric	245000	Nil	0	21	No	CM	CR

12	Ravi	37/M	Attur	Rt ankle	1hr 45 mins	No	No	Yes	Yes	> 20	Yes	No	1	non-oliguric	215000	Nil	0	24	No	CM	CR
13	Namagiriyammal	70/M	Namakkal	Lt foot	2 hrs	No	No	Yes	No	> 20	No	No	2	non-oliguric	180000	Trace	3	18	No	CM	CR
14	Saroja	50/F	Salem	Lt foot	50 mins	SHT	No	No	No	>20	No	No	1	non-oliguric	210000	1+	0	8	No	CM	CR
15	Backiyam	53/F	Valapadi	Lt foot	13 hrs	No	No	Yes	Yes	> 20	No	No	2	oliguric	15000	3+	2	8	Yes	Dialysis	CR
16	Jeya Prakash	40/M	Namakkal	Rt foot	8 hrs 15 mins	PLHA	No	Yes	No	> 20	No	No	2	non-oliguric	30000	2+	2	16	No	CM	CR
17	Sundar	37/M	Vedakuthapatti	Lt foot	10 hrs 40 mins	SHT	No	No	No	>20	No	No	1	non-oliguric	240000	Nil	0	8	No	CM	CR
18	Senkodan	50/M	Namakkal	Lt foot	30 mins	No	No	No	No	> 20	No	No	1	non-oliguric	240000	Nil	0	16	No	CM	CR
19	Esther Divya	21/F	Erode	Rt foot	4 hrs	No	No	Yes	Yes	< 20	No	No	1	non-oliguric	82000	3+	1	30	No	CM	CR

20	Saravanan	21/M	Salem	Rt hand	2 hrs	No	No	No	No	>20	No	No	1	non-oliguric	240000	Nil	0	8	No	CM	CR
21	Ramalingam	27/M	Salem	Rt ankle	50 mins	No	No	No	No	>20	No	No	1	non-oliguric	240000	Nil	0	8	No	CM	CR
22	Kannammal	70/F	Rasipuram	Lt hand	1 hr 40 mins	SHT/ DM	No	Yes	Yes	< 20	No	No	4	non-oliguric	70000	3+	3	15	No	CM	CR
23	Manikodi	38/F	Salem	rt foot	2 hrs	No	No	No	No	> 20	No	No	1	non-oliguric	240000	Nil	0	13	No	CM	CR
24	Sarasu	55/F	Namakkal	Lt foot	2 hrs 45 mins	No	No	Yes	No	< 20	Yes	Yes	1	non-oliguric	225000	1+	0	24	No	MV	DEATH
25	Ramayee	27/F	Omalur	Rt foot	1 hr 45 mins	No	No	Yes	Yes	> 20	Yes	No	1	non-oliguric	270000	1+	1	30	No	CM	CR
26	Kannappan	55/M	Rasipuram	Lt foot	2 hr	No	No	Yes	Yes	> 20	No	No	2	non-oliguric	60000	Nil	2	13	No	CM	CR
27	Sekar	36/M	Namakkal	Lt foot	1 hr	No	No	Yes	Yes	> 20	No	No	1	non-oliguric	310000	Nil	1	16	Yes	CM	CR

28	Palaniyammal	55/ F	Attur	Rt hand	1 hr	No	No	Yes	No	> 20	No	No	1	non-oliguric	410000	Nil	0	16	No	CM	CR
29	Nithya	22/F	Omalur	Rt hand	1 hr	No	No	No	No	>20	No	No	1	non-oliguric	280000	Nil	0	5	No	CM	CR
30	Marappan	50/M	Salem	Lt hand	2 hrs 25 mins	No	No	No	No	>20	No	No	1	non-oliguric	310000	Nil	0	5	No	CM	CR
31	Mani	50/M	Salem	Rt foot	4 hrs 30 mins	No	No	Yes	Yes	< 20	No	No	1	non-oliguric	350000	Nil	0	21	No	CM	CR
32	Sujatha	32/F	Salem	Rt shoulder	30 mins	No	No	No	No	> 20	No	No	1	non-oliguric	215000	Nil	1	16	No	CM	CR
33	Rajammal	60/F	Erode	Lt foot	1 hr	SHT	No	Yes	Yes	> 20	No	No	3	oliguric	30000	2+	3	30	No	Dialysis	DD
34	Ramasamy	60/M	Rasipuram	Rt foot	8 HRS	No	No	yes	Yes	> 20	no	no	3	non-oliguric	145000	Nil	3	16	No	CM	CR
35	Velu	50/M	Chinnasalem	Rt foot	2 HRS	No	No	Yes	Yes	> 20	No	No	1	non-oliguric	190000	Nil	0	21	No	CM	CR

36	Palanisamy	25/M	Salem	Lt foot	30 mins	No	No	Yes	Yes	>20	Yes	No	1	non-oliguric	260000	Nil	0	13	No	CM	CR
37	Thangam	40/F	Krishnagiri	Lt foot	12 HRS	No	No	Yes	Yes	< 20	No	No	1	non-oliguric	260000	Nil	2	21	No	CM	CR
38	Murugesan	45/M	Namakkal	Lt foot	12 HRS	No	No	Yes	Yes	< 20	No	No	2	oliguric	30000	1+	3	32	No	Dialysis	CR
39	Govindharaj	40/M	Attur	Rt foot	3HRS 30 MINS	No	No	Yes	Yes	> 20	No	No	1	non-oliguric	380000	Nil	0	13	No	CM	CR
40	Vijayakumar	34/M	Salem	Lt hand	2 hrs 30 mins	No	No	Yes	No	< 20	No	No	1	non-oliguric	160000	Nil	0	5	No	CM	CR
41	Pappathi	50/F	Salem	Rt hand	1 hr	No	No	Yes	No	< 20	No	No	1	non-oliguric	210000	Nil	0	5	No	CM	CR
42	Valliammal	35/F	Erode	Lt foot	2 hrs	No	No	Yes	Yes	> 20	No	No	1	non-oliguric	280000	Nil	0	21	No	CM	CR
43	Saraswathi	40/F	Rasipuram	Lt foot	2 hrs	No	No	Yes	No	< 20	No	No	1	non-oliguric	240000	Nil	0	5	No	CM	CR

44	Nallathambi	61/M	Omalur	Rt foot	1 HR	No	No	Yes	Yes	> 20	No	No	1	non-oliguric	160000	Nil	0	21	No	CM	CR
45	Kannan	46/F	Chinnasalem	Lt foot	3 hrs	No	No	Yes	Yes	> 20	Yes	No	1	non-oliguric	160000	Nil	0	23	No	CM	CR
46	Chinnaiyan	52/M	Attur	Rt foot	56 mins	No	No	Yes	Yes	> 20	No	No	1	oliguric	20000	3+	3	18	No	CM	CR
47	Arayee	53/F	Mettur	Lt foot	2 HRS	No	No	Yes	Yes	< 20	No	No	1	non-oliguric	350000	Nil	0	5	No	CM	CR
48	Soundarya	18/F	Salem	Rt foot	1 HR	No	No	Yes	Yes	> 20	Yes	No	1	non-oliguric	210000	Nil	0	13	No	CM	CR
49	Govindhan	55/M	Omalur	Lt foot	2 HRS	No	No	Yes	Yes	> 20	Yes	No	1	non-oliguric	210000	Nil	0	33	No	CM	CR
50	vadivel	56/m	attur	rt foot	8 hrs	no	yes	yes	yes	>20	no	no	2	oliguric	50000	3+	3	28	no	dialysis	CR
51	gandhiammal	80/f	rasipuram	rt foot	1 hr	no	no	Yes	no	<20	yes	yes	1	non-oliguric	150000	nil	0	20	No	CM	CR

52	Elavarasan	30/F	Attur	Rt foot	2.30 Hrs	No	NO	YES	YES	>20	NO	NO	2	oliguric	50000	3+	3	32	No	CM	DEATH
53	KUMARESAN	25/M	ATTUR	RT FOOT	2.30 HRS	NO	NO	YES	YES	>20	YES	NO	1	non-oliguric	80000	3+	2	30	NO	CM	CR
54	KANDHASAMY	60/M	KALLAKURICHI	LT FOOT	2 HRS	NO	NO	YES	YES	>20	NO	NO	5	oliguric	40000	3+	3	28	NO	Dialysis	DEATH
55	MUTHUSAMY	20/M	SALEM	RT SHOULDER	2 HRS	NO	NO	NO	NO	>20	NO	NO	1	non-oliguric	180000	Nil	0	10	NO	CM	CR
56	MEENA	17/F	Rasipuram	RT FOOT	1/2 HRS	NO	NO	YES	YES	>20	NO	NO	1	non-oliguric	280000	NIL	0	21	No	CM	CR
57	GOVINDHARAJ	50/F	Salem	RT FOOT	2 HRS	NO	No	Yes	NO	<20	NO	NO	1	non-oliguric	210000	Nil	0	5	NO	CM	CR
58	VENKATACHALAM	29/F	SALEM	RT HAND	7 HRS	NO	NO	NO	Yes	<20	NO	NO	1	non-oliguric	240000	NIL	0	5	NO	CM	CR
59	GANABATHI	63/M	SALEM	RT FOOT	11/2 HRS	No	No	YES	YES	>20	NO	NO	2	non-oliguric	160000	Trace	1	23	NO	CM	CR

60	SIVAKUMAR	25/M	KALLAKURICHI	RT FOOT	2 HRS	NO	NO	YES	YES	<20	NO	NO	2	non-oliguric	20000	3+	2	25	No	CM	CR
61	ARUKKANI	65/F	Rasipuram	Lt foot	1 HR	SHT	NO	Yes	Yes	>20	NO	NO	1	non-oliguric	210000	Nil	0	8	No	CM	CR
62	PERUMAYEE	60/F	Salem	LT FOOT	1 HR	NO	NO	NO	NO	>20	NO	NO	1	non-oliguric	150000	Nil	0	8	No	CM	CR
63	NATARAJAN	65/M	Valapadi	RT FOOT	1 HR	NO	NO	Yes	NO	<20	NO	No	1	non-oliguric	210000	Nil	0	5	No	CMC	CR
64	MENAKA	35/F	OMALUR	RT LEG	6 HRS	No	No	Yes	No	>20	Yes	NO	1	non-oliguric	250000	Nil	0	20	NO	CM	CR
65	RAMESH	32/M	DHARMAPURI	RT HAND	2 HRS	NO	NO	YES	NO	>20	NO	NO	2	non-oliguric	30000	3+	3	28	No	Dialysis	CR
66	SARASWATHY	52/F	Rasipuram	LT FOOT	1 HR	SHT	NO	No	No	>20	No	No	2	oliguric	200000	3+	3	30	NO	Dialysis	DD
67	VENKATACHALAM	35/M	Valapadi	rt foot	1 HR	NO	NO	Yes	YES	>20	No	No	1	non-oliguric	420000	NIL	0	16	No	CM	CR

68	MANIVANNAN	20/M	TIRUPUR	LT FOOT	3 HRS	No	No	Yes	No	>20	Yes	Yes	1	non-oliguric	150000	Nil	0	25	No	CM	CR
69	ANANDHAN	60/M	Rasipuram	RT LEG	1 HR	No	Yes	Yes	Yes	>20	Yes	No	3	oliguric	49000	1+	3	23	No	Dialysis	DEATH
70	PERUMAL	24/m	Salem	rt hand	4 hrs	No	No	Yes	Yes	>20	No	No	2	non-oliguric	250000	Nil	1	23	No	CM	CR
71	selvi	15/f	Rasipuram	rt foot	2 hrs	No	No	Yes	No	<20	Yes	Yes	1	non-oliguric	230000	Nil	0	24	No	MV	DEATH
72	padmavathy	55/F	Salem	RT FOOT	58 HRS	SHT	No	YES	NO	<20	No	No	4	oliguric	20000	3+	3	8	No	Dialysis	DD
73	JAYAPRADHA	46/F	Salem	LT HAND	1 HR	No	No	Yes	No	<20	No	No	1	non-oliguric	240000	Nil	0	5	No	CM	CR
74	GURUSAMY	50/M	Erode	LT FOOT	1 HR	No	No	Yes	Yes	<20	No	No	1	non-oliguric	150000	Nil	1	23	No	CM	CR
75	PALANIYAPPAN	52/M	Salem	RT FOOT	1 1/2 HRS	No	No	Yes	Yes	>20	No	No	3	non-oliguric	60000	4+	3	28	No	CM	CR

76	PARASURAMAN	34/M	NAMAKKAL	RT FOOT	6 HRS	NO	NO	YES	YES	>20	NO	NO	1	oliguric	75000	1+	3	36	NO	Dialysis	CR
77	SARAVANAN	39/M	Salem	RT FOOT	51/2 HRS	NO	NO	YES	YES	>20	YES	NO	1	non-oliguric	220000	Nil	0	30	No	CM	CR
78	VENNILA	44/M	Salem	LT FOOT	1HR	NO	NO	NO	NO	>20	No	NO	1	non-oliguric	300000	Nil	0	5	No	CM	CR
79	TAMILSELVAN	29/M	Rasipuram	Rt hand	3 HRS	No	No	Yes	Yes	>20	No	No	1	non-oliguric	100000	1+	1	13	No	CM	CR
80	VIGNESH	21/M	Salem	RT FOOT	81/2 HRS	NO	No	Yes	Yes	>20	No	No	1	non-oliguric	140000	Nil	0	30	No	CM	CR
81	YASOTHA	70/F	Salem	Rt ankle	51/2 HRS	HTN	NO	YES	YES	>20	NO	NO	1	oliguric	190000	2+	3	28	No	Dialysis	DD
82	BABU	30/M	Salem	Rt hand	4 HRS	No	No	Yes	Yes	>20	No	No	1	oliguric	110000	3+	3	28	No	Dialysis	CR
83	SAROJA	57/F	Valapadi	RT FOOT	2 HRS	No	No	No	NO	>20	No	No	1	non-oliguric	190000	0	0	5	No	CM	CR

84	RASIKA	17/F	Salem	RT FOOT	2 HRS	No	No	No	No	>20	Yes	No	1	non-oliguric	160000	Nil	0	5	No	CM	CR
85	VAITHY GOUNDAR	25/M	SANKAGIRI	RT FOOT	10 1/2 HRS	No	No	Yes	Yes	>20	No	No	3	oliguric	60000	3+	3	28	No	Dialysis	DD
86	NAKESH	21/M	DHARMAPURI	LT FOOT	2 HRS	No	No	Yes	Yes	>20	No	No	3	oliguric	70000	2+	3	32	No	Dialysis	CR
87	Murugesan	40/M	Salem	RT LEG	21/2 HRS	No	No	Yes	Yes	>20	No	No	``2.1	oliguric	125000	1+	2	30	NO	Dialysis	CR
88	BANUPRIYA	21/F	Salem	RT FOOT	2 HRS	No	No	Yes	Yes	<20	Yes	Yes	1	non-oliguric	250000	0	0	20	No	MV	CR
89	VYUVARAJ	17/M	Salem	RT LEG	1 HR	No	No	Yes	No	>20	No	No	1	non-oliguric	280000	0	0	5	No	CM	CR
90	SAHANKAR	29/M	DHARMAPURI	RT LEG	1 HRS	No	No	Yes	Yes	>20	No	No	1	non-oliguric	170000	Trace	0	30	No	CM	CR
91	GANABATHI	63/M	KALLAKURICHI	RT FOOT	1/2 HRS	No	No	Yes	No	>20	No	No	1	non-oliguric	220000	Nil	0	33	No	CM	CR

92	GANAGAMALAI	42/F	Namakkal	RT LEG	31/2 HRS	No	No	Yes	No	>20	No	No	1	non-oliguric	370000	Nil		0	15	No	CM	CR
93	THANGAMALAI	52/F	Omalur	Rt ankle	11/2 HRS	No	No	Yes	Yes	>20	No	No	1	oliguric	15000	3+		3	30	No	Dialysis	DD
94	PREMKUMAR	19/M	Mettur	LT FOOT	2 HRS	No	No	Yes	Yes	>20	No	No	1	non-oliguric	120000		0	0	20	No	CM	CR
95	Raja	38/M	Rasipuram	RT HAND	21/2 HRS	No	No	Yes	Yes	>20	No	No	1	non-oliguric	190000		0	0		No	CM	CR
96	KARAN	16/M	MECHERY	RT FOOT	3 HRS	No	No	Yes	Yes	>20	No	No	1	non-oliguric	160000		0	0	20	No	CM	CR
97	ESHWARI	24/F	SALEM	RT FOOT	21/2 HRS	No	No	No	No	>20	No	No	1	non-oliguric	190000		0	0	5	No	CM	CR
98	MEENA	18/F	Salem	RT FOOT	21/2 HRS	No	No	Yes	No	<20	No	No	1	non-oliguric	180000		0	0	5	No	CM	CR
99	BOOPATHY	70/M	Salem	RT FOOT	33 HRS	No	No	Yes	Yes	>20	No	No	5	oliguric	20000	3+		3	30	No	Dialysis	DEATH

100	RAMASAMY	47/M	MECHERY	RT LEG	21/2 HRS	No	No	Yes	Yes	>20	No	No	1	non-oliguric	260000	1+	1	33	No	CM	CR